

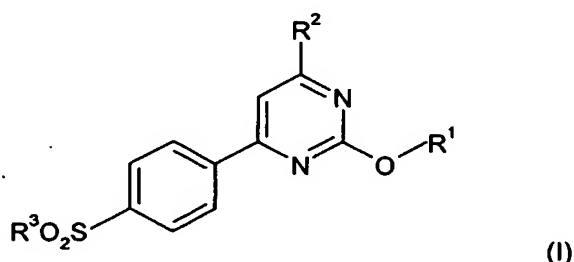
USE OF CYCLOOXYGENASE-2 SELECTIVE INHIBITORS FOR THE TREATMENT OF SCHIZOPHRENIC DISORDERS

The invention concerns the use of compounds, which are selective COX-2 (cyclooxygenase-2) inhibitors, for the treatment of schizophrenic disorders.

Schizophrenic disorders of the invention include schizophrenia, delusional disorders, affective disorders, autism or tic disorders, schizophreniform disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses and temporary acute psychotic disorders.

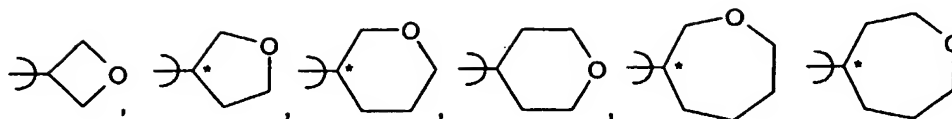
Moreover, the invention is concerned with the use of a compound of the present invention in combination with a neuroleptic drug for the treatment of the above mentioned schizophrenic disorders.

In one embodiment, the present invention provides a new use of compounds of formula (I)



and pharmaceutically acceptable salts or solvates thereof, wherein

- R¹ is selected from the group consisting of H, C₁₋₆alkyl, C₁₋₂alkyl substituted by one to five fluorine atoms, C₃₋₆alkenyl, C₃₋₆alkynyl, C₃₋₁₀cycloalkylC₀₋₆alkyl, C₄₋₁₂bridged cycloalkyl, A(CR⁴R⁵)_n and B(CR⁴R⁵)_n;
- R² is C₁₋₂alkyl substituted by one to five fluorine atoms;
- R³ is selected from the group consisting of C₁₋₆alkyl, NH₂ and R⁷CONH;
- R⁴ and R⁵ are independently selected from H or C₁₋₆alkyl;
- A is selected from the group consisting of unsubstituted 5- or 6-membered heteroaryl, unsubstituted 6-membered aryl, 5- or 6-membered heteroaryl substituted by one or more R⁶ and 6-membered aryl substituted by one or more R⁶;
- R⁶ is selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted by one more fluorine atoms, C₁₋₆alkoxy, C₁₋₆alkoxy substituted by one or more F, NH₂SO₂ and C₁₋₆alkylSO₂;
- B is a ring selected from the group consisting of



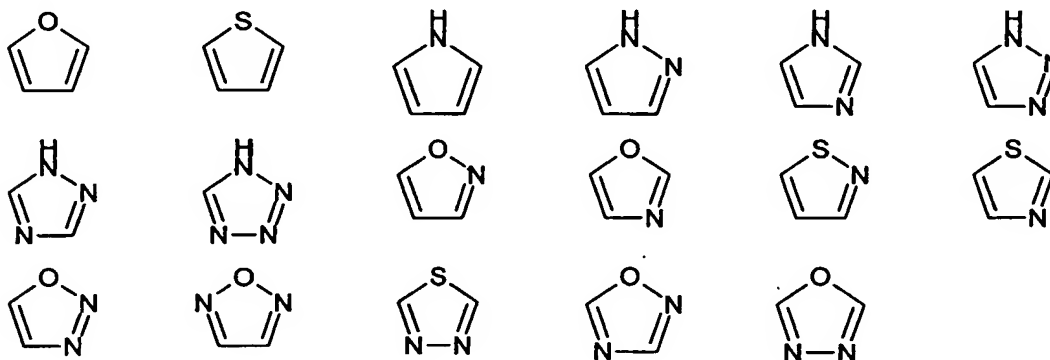
where  defines the point of attachment of the ring;

R^7 is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylOC $_{1-6}$ alkyl, phenyl, HO $_2$ CC $_{1-6}$ alkyl, C_{1-6} alkylOCOC $_{1-6}$ alkyl, C_{1-6} alkylOCO, H $_2$ NC $_{1-6}$ alkyl, C_{1-6} alkylOCONHC $_{1-6}$ alkyl and C_{1-6} alkylCONHC $_{1-6}$ alkyl; and
 n is 0 to 4.

The term halogen is used to represent fluorine, chlorine, bromine or iodine.

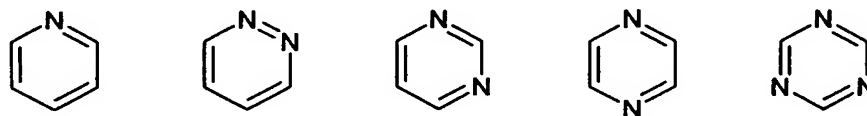
- 10 The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

The term 5-membered heteroaryl means a heteroaryl selected from the following:

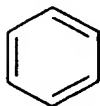


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The term 6-membered heteroaryl means a heteroaryl selected from the following:



The term 6-membered aryl means:



It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). In particular when the ring B lacks a plane of symmetry the compounds of formula (I) contain a chiral centre as indicated therein by the asterisk *. Furthermore, it will be appreciated by those skilled in the art that when R^4 and R^5 in formula (I) are different the corresponding compounds contain at least one chiral centre, by virtue of the asymmetric carbon atom defined thereby, and that such compounds exist in the form of a pair of optical isomers (i.e. enantiomers).

In one aspect of the invention R^1 is selected from the group consisting of H, C_{1-6} alkyl, C_{1-2} alkyl substituted by one to five fluorine atoms, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkyl, C_{4-12} bridged cycloalkyl and $B(CR^4R^5)_n$.

In another aspect of the invention R^1 is C_{1-6} alkyl or C_{1-2} alkyl substituted by one to five fluorine atoms. In another aspect R^1 is C_{2-6} alkyl (e.g. n-butyl).

In another aspect of the invention R^1 is C_{3-10} cycloalkyl, such as C_{3-10} cycloalkyl (e.g. cyclopentyl or cyclohexyl). In another aspect R^1 is C_{3-10} cycloalkylmethyl, such as C_{3-7} cycloalkylmethyl (e.g. cyclopentylmethyl).

In another aspect of the invention R^1 is $A(CR^4R^5)_n$.

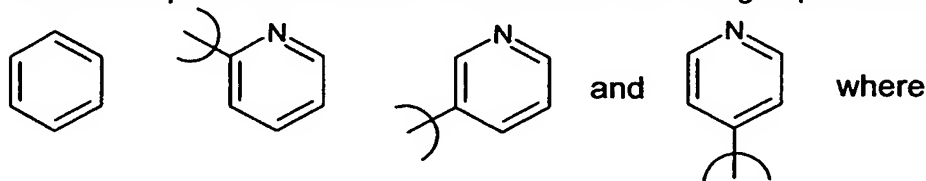
In another aspect of the invention R^2 is CHF_2 , CH_2F or CF_3 . In another aspect R^2 is CF_3 .

In another aspect of the invention R^3 is C_{1-6} alkyl, such as C_{1-3} alkyl (e.g. methyl).

In another aspect of the invention R^4 and R^5 are independently selected from H or methyl.

In another aspect R^4 and R^5 are both H.

In another aspect of the invention A is selected from the group consisting of



) defines the point of attachment of the ring

and A is unsubstituted or substituted by one or two R^6 .

In another aspect of the invention R^6 is selected from the group consisting of halogen (e.g. F), C_{1-3} alkyl (e.g. methyl), C_{1-3} alkyl substituted by one to three fluorine atoms (e.g. CF_3), and C_{1-3} alkoxy (e.g. methoxy).

In another aspect of the invention R^7 is selected from the group consisting of C_{1-6} alkyl (e.g. ethyl), phenyl and aminomethyl.

In another aspect of the invention n is 1 to 4.

In another aspect of the invention n is 0 to 2 (e.g. 0).

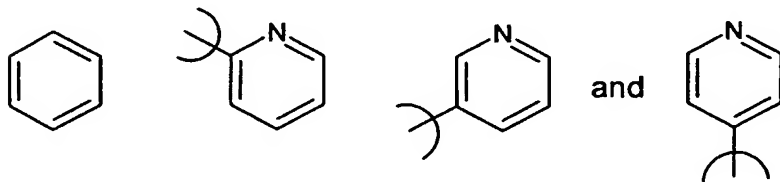
- 5 It is to be understood that the invention covers all combinations of particular aspects of the invention as described hereinabove.

Within the invention there is provided one group of compounds of formula (I) (group A) wherein: R^1 is C_{1-6} alkyl (e.g. n-butyl); R^2 is CF_3 ; and R^3 is C_{1-6} alkyl, such as C_{1-3} alkyl (e.g. methyl).

- 10 Within the invention there is provided another group of compounds of formula (I) (group B) wherein: R^1 is C_{3-10} cycloalkyl C_{0-6} alkyl, such as C_{3-10} cycloalkyl (e.g. cyclopentyl or cyclohexyl); R^2 is CF_3 ; and R^3 is C_{1-6} alkyl, such as C_{1-3} alkyl (e.g. methyl).

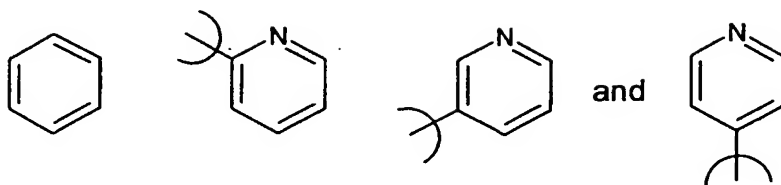
- 15 Within the invention there is provided another group of compounds of formula (I) (group C) wherein: R^1 is C_{3-10} cycloalkylmethyl, such as C_{3-7} cycloalkylmethyl (e.g. cyclopentylmethyl); R^2 is CF_3 ; and R^3 is C_{1-6} alkyl, such as C_{1-3} alkyl (e.g. methyl).

Within the invention there is provided another group of compounds of formula (I) (group D) wherein: R^1 is $A(CR^4R^5)_n$; R^2 is CF_3 ; R^3 is C_{1-6} alkyl, such as C_{1-3} alkyl (e.g. methyl); R^4 and R^5 are independently selected from H or methyl; A is selected from the group consisting of



and A is unsubstituted or substituted by one or two R^6 ; R^6 is selected from the group consisting of halogen (e.g. F), C_{1-3} alkyl (e.g. methyl), C_{1-3} alkyl substituted by one to three fluorine atoms (e.g. CF_3), and C_{1-3} alkoxy (e.g. methoxy); and n is 0 to 2 (e.g. 0).

- 25 Within group D, there is provided a further group of compounds (group D1) wherein: R^1 is $A(CR^4R^5)_n$; R^2 is CF_3 ; R^3 is methyl; R^4 and R^5 are both H; A is selected from the group consisting of



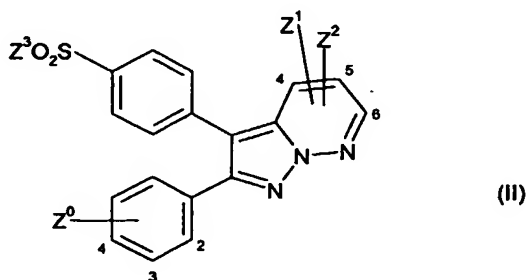
and A is unsubstituted or substituted by one or two R^6 ; R^6 is selected from the group consisting of fluorine, chlorine, methyl, CF_3 and methoxy; and n is 0 or 1.

- 5 Compounds of formula (I) and salts and solvates thereof are described in PCT publication No. WO02/096885, published 5 December 2002 and US Appl. Serial N° 10/477547, published 2 September 2004. The disclosures of these references are incorporated herein by reference in their entirety. Compounds of formula (I) may be prepared by any method described in WO 02/096885, US Appl. Serial N° 10/477547 and equivalent patent
10 applications.

In a further embodiment, the present invention provides compounds of formula (I) and pharmaceutically acceptable salts or solvates thereof, for use in the preparation of a medicament for the treatment of schizophrenic disorders as defined above.

- 15 In another embodiment, the present invention provides a method for the treatment of schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary acute psychotic disorders comprising administering a therapeutically effective amount of a
20 compound of formula (I) or a pharmaceutically acceptable salts or solvates thereof.

In a one embodiment, the present invention provides a new use of compounds of formula (II)



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and pharmaceutically acceptable salts or solvates thereof, wherein

- Z^0 is selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy substituted by one or more fluorine atoms, and $O(CH_2)_nNZ^4Z^5$;
- Z^1 and Z^2 are each the same or different and are independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkyl substituted by one or more fluorine atoms, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, SC_{1-6} alkyl, $C(O)H$, $C(O)C_{1-6}$ alkyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxy substituted by one or more fluorine atoms, $O(CH_2)_nCO_2C_{1-6}$ alkyl, $O(CH_2)_nSC_{1-6}$ alkyl, $(CH_2)_nNZ^4Z^5$, $(CH_2)_nSC_{1-6}$ alkyl and $C(O)NZ^4Z^5$;
- with the proviso that when Z^0 is at the 4-position and is halogen, then at least one of Z^1 and Z^2 is C_{1-6} alkylsulphonyl, C_{1-6} alkoxy substituted by one or more fluorine atoms, $O(CH_2)_nCO_2C_{1-6}$ alkyl, $O(CH_2)_nSC_{1-6}$ alkyl, $(CH_2)_nNZ^4Z^5$, $(CH_2)_nSC_{1-6}$ alkyl or $C(O)NZ^4Z^5$;
- Z^3 is C_{1-6} alkyl or NH_2 ;
- Z^4 and Z^5 are each the same or different and are independently selected from the group consisting of H, or C_{1-6} alkyl or, Z^4 and Z^5 together with the nitrogen atom to which they are bound, form a 4 - 8 membered saturated heterocyclic ring having 1 or 2 heteroatoms selected from N, O and S; and
- n^1 is 1-4.

The term halogen is used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

- Preferably, Z^0 is at the 3- or 4-position of the phenyl ring, as defined in formula (I).

Preferably, Z^1 is at the 6-position of the pyridazine ring, as defined in formula (I).

Preferably, Z^0 is F, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkoxy substituted by one or more fluorine atoms, or $O(CH_2)_{1-3}NZ^4Z^5$. More preferably Z^0 is F, C_{1-3} alkoxy or C_{1-3} alkoxy substituted by one or more fluorine atoms.

- Preferably, Z^1 is C_{1-4} alkylsulphonyl, C_{1-4} alkoxy substituted by one or more fluorine atoms, $O(CH_2)_{1-3}CO_2C_{1-4}$ alkyl, $O(CH_2)_{1-3}SC_{1-4}$ alkyl, $(CH_2)_{1-3}NZ^4Z^5$, $(CH_2)_{1-3}SC_{1-4}$ alkyl or $C(O)NZ^4Z^5$ or, when Z^0 is C_{1-6} alkyl, C_{1-6} alkoxy, $O(CH_2)_nNZ^4Z^5$, may also be H. More preferably Z^1 is C_{1-4} alkylsulphonyl, C_{1-4} alkoxy substituted by one or more fluorine atoms or, when Z^0 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy substituted by one or more fluorine atoms, or $O(CH_2)_nNZ^4Z^5$, may also be H.

Preferably, Z^2 is H.

Preferably, Z^3 is methyl or NH_2 .

Preferably Z^4 and Z^5 are independently C_{1-3} alkyl or, together with the nitrogen atom to which they are attached, form a 5 - 6 membered saturated ring.

- 5 Preferably, n is 1 - 3, more preferably 1 or 2.

Within the invention there is provided one group of compounds of formula (I) (group A1) and pharmaceutically acceptable salts or solvates thereof, wherein: Z^0 is F, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkoxy substituted by one or more fluorine atoms, or $O(CH_2)_nNZ^4Z^5$; Z^1 is C_{1-4} alkylsulphonyl, C_{1-4} alkoxy substituted by one or more fluorine atoms, $O(CH_2)_nCO_2C_{1-4}$ alkyl, $O(CH_2)_nSC_{1-4}$ alkyl, $(CH_2)_nNZ^4Z^5$, $(CH_2)_nSC_{1-4}$ alkyl or $C(O)NZ^4Z^5$ or, when Z^0 is C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkoxy substituted by one or more fluorine atoms, or $O(CH_2)_nNZ^4Z^5$, may also be H; Z^2 is H; R^3 is methyl or NH_2 ; Z^4 and Z^5 are independently C_{1-3} alkyl or, together with the nitrogen atom to which they are attached, form a 5 - 6 membered saturated ring; and n is 1 - 3.

- 15 Within group A, there is provided another group of compounds (group A2) and pharmaceutically acceptable salts or solvates thereof, wherein Z^0 is F, methyl, C_{1-2} alkoxy, $OCHF_2$, or $O(CH_2)_nNZ^4Z^5$; Z^1 is methylsulphonyl, $OCHF_2$, $O(CH_2)_nCO_2C_{1-4}$ alkyl, $O(CH_2)_nSCH_3$, $(CH_2)_nNZ^4Z^5$, $(CH_2)_nSCH_3$ or $C(O)NZ^4Z^5$ or, when Z^0 is methyl, C_{1-2} alkoxy, $OCHF_2$, or $O(CH_2)_nN(CH_3)_2$, may also be H; Z^2 is H; Z^3 is methyl or NH_2 ; Z^4 and Z^5 are both methyl or, together with the nitrogen atom to which they are attached, form a 5 - 6 membered saturated ring; and n is 1 - 2.

- 25 Within group A, there is provided a further group of compounds (group A3), and pharmaceutically acceptable salts or solvates thereof wherein Z^0 is F, C_{1-3} alkoxy or C_{1-3} alkoxy substituted by one or more fluorine atoms; Z^1 is C_{1-4} alkylsulphonyl, C_{1-4} alkoxy substituted by one or more fluorine atoms or, when Z^0 is C_{1-3} alkoxy or C_{1-3} alkoxy substituted by one or more fluorine atoms, may also be H; Z^2 is H; and Z^3 is methyl or NH_2 .

Within groups A1, A2 and A3, Z^0 is preferably at the 3- or 4-position of the phenyl ring and Z^1 is preferably at the 6-position of the pyridazine ring.

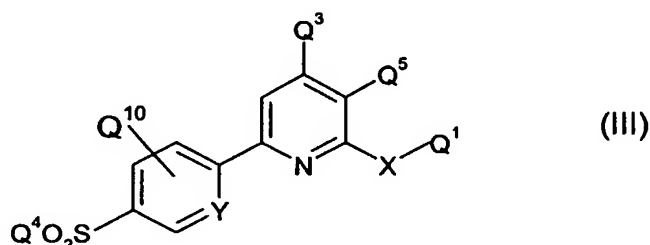
- 30 Compounds of formula (II) and pharmaceutically acceptable salts and solvates thereof are described in PCT publication No. WO 99/12930, published 18 March 1999 and US Patent N° 6,451,794, US-A-2003-0040517 and US-A-2003-0008872. The disclosures of these references are incorporated herein by reference in their entirety. Compounds of formula (II) may be prepared by any method described in WO 99/12930, US Patent N° 6,451,794,

US-A-2003-0040517 and US-A-2003-0008872 and equivalent patent applications.

In a further embodiment, the present invention provides compounds of formula (II) and pharmaceutically acceptable salts or solvates thereof, for use in the preparation of a medicament for the treatment of schizophrenic disorders as defined above.

In another embodiment, the present invention provides a method for the treatment of schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary acute psychotic disorders comprising administering a therapeutically effective amount of a compound of formula (II) or a pharmaceutically acceptable salts or solvates thereof.

In one embodiment the present invention provides a new use of compounds of formula (III)



and pharmaceutically acceptable salts or solvates thereof, wherein:

- | | |
|----|--|
| 20 | <p>X is selected from the group consisting of oxygen or NQ²;</p> <p>Y is selected from the group consisting of CH or nitrogen;</p> <p>Q¹ is selected from the group consisting of H, C₁₋₆alkyl, C₁₋₂alkyl substituted by one to five fluorine atoms, C₁₋₃alkylOC₁₋₃alkyl, C₃₋₆alkenyl, C₃₋₆alkynyl, C₃₋₁₀cycloalkylC₀₋₆alkyl, C₄₋₇cycloalkyl substituted by C₁₋₃alkyl or C₁₋₃alkoxy, C₄₋₁₂bridged cycloalkyl, A(CR⁶R⁷)_n and B(CR⁶R⁷)_n;</p> |
| 25 | <p>Q² is selected from the group consisting of H and C₁₋₆alkyl; or</p> <p>Q¹ and Q² together with the nitrogen atom to which they are attached form a 4-8 membered saturated heterocyclic ring such as a pyrrolidine, morpholine or piperidine ring, or a 5-membered heteroaryl ring which is unsubstituted or substituted by one R⁸;</p> |
| 30 | <p>Q³ is selected from the group consisting of C₁₋₅alkyl and C₁₋₂alkyl substituted by one to five fluorine atoms;</p> <p>Q⁴ is selected from the group consisting of C₁₋₆alkyl, NH₂ and R⁹CONH;</p> |

Q⁵ is selected from the group consisting of hydrogen, C₁₋₃alkyl, C₁₋₂alkyl substituted by one to five fluorine atoms, C₁₋₃alkylO₂C, halogen, cyano, (C₁₋₃alkyl)₂NCO, C₁₋₃alkylS and C₁₋₃alkylO₂S;

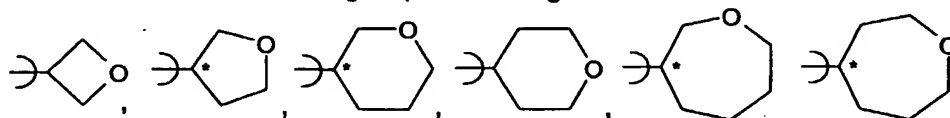
Q⁶ and Q⁷ are independently selected from H or C₁₋₆alkyl;

5 A¹ is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R⁸;

Q⁸ is selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted by one more fluorine atoms, C₁₋₆alkoxy, C₁₋₆alkoxy substituted by one or more F, NH₂SO₂ and C₁₋₆alkylSO₂;

10

B¹ is selected from the group consisting of



and where) defines the point of attachment of the ring;

Q⁹ is selected from the group consisting of H, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, phenyl, HO₂CC₁₋₆alkyl, C₁₋₆alkylOCOC₁₋₆alkyl, C₁₋₆alkylOCO, H₂NC₁₋₆alkyl, C₁₋₆alkylOCONHC₁₋₆alkyl and C₁₋₆alkyl CONHC₁₋₆alkyl;

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Q¹⁰ is selected from the group consisting of H and halogen; and n is 0 to 4;

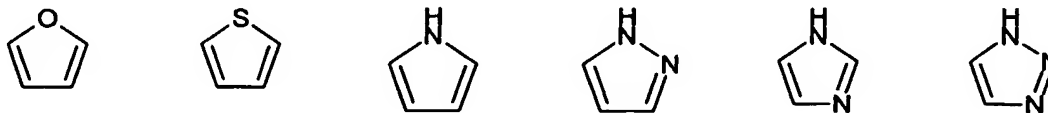
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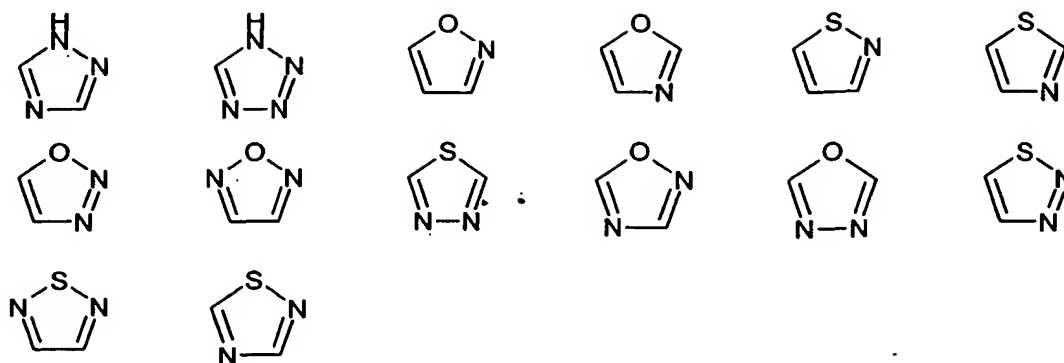
The term 'halogen' is used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

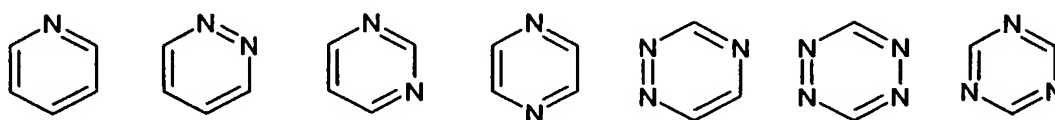
25 The term 'saturated heterocyclic' means a saturated ring containing at least one atom other than carbon.

The term '5-membered heteroaryl' means a heteroaryl selected from the following:

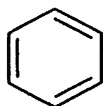




The term '6- membered heteroaryl' means a heteroaryl selected from the following:

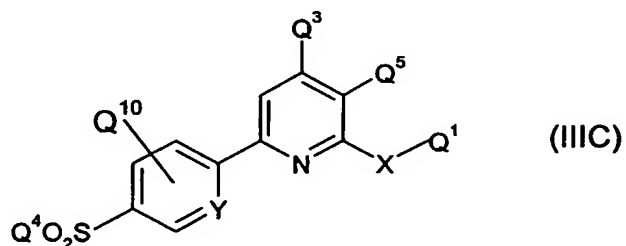


The term '6-membered aryl' means:



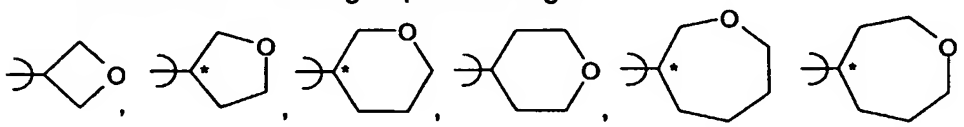
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Compound of formula (III) may be a compound of formula (IIIC)

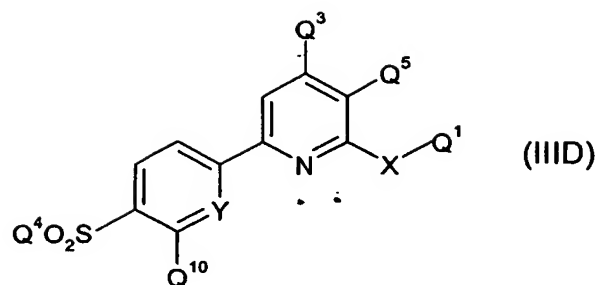


and pharmaceutically acceptable salts or solvates thereof, wherein

- 10 X is selected from the group consisting of oxygen or NR²;
 Y is selected from the group consisting of CH or nitrogen;
 Q¹ is selected from the group consisting of H, C₁₋₆alkyl, C₁₋₂alkyl substituted
 by one to five fluorine atoms, C₁₋₃alkylOC₁₋₃alkyl, C₃₋₆alkenyl, C₃₋₆alkynyl,

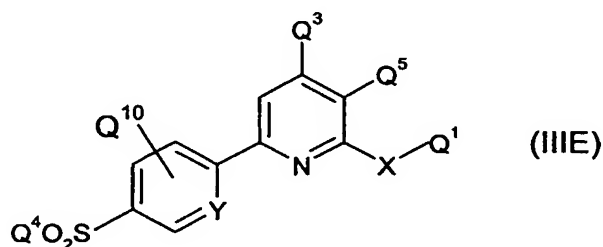
- C_{3-10} cycloalkyl C_{0-6} alkyl, C_{4-12} bridged cycloalkyl, $A(CQ^6Q^7)_n$ and $B(CQ^6Q^7)_n$;
- 5 Q^2 is selected from the group consisting of H and C_{1-6} alkyl; or
- Q^1 and Q^2 together with the nitrogen atom to which they are attached form a 4-8 membered saturated heterocyclic ring such as a pyrrolidine, morpholine or piperidine ring;
- Q^3 is selected from the group consisting of C_{1-5} alkyl and C_{1-2} alkyl substituted by one to five fluorine atoms;
- 10 Q^4 is selected from the group consisting of C_{1-6} alkyl, NH_2 and Q^9CONH ;
- Q^5 is selected from the group consisting of hydrogen, C_{1-3} alkyl, C_{1-2} alkyl substituted by one to five fluorine atoms, halogen, cyano, $(C_{1-3}alkyl)_2NCO$, $C_{1-3}alkylS$ and $C_{1-3}alkylO_2S$;
- Q^6 and Q^7 are independently selected from H or C_{1-6} alkyl;
- 15 A^1 is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more Q^8 ;
- Q^8 is selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkyl substituted by one more fluorine atoms, C_{1-6} alkoxy, C_{1-6} alkoxy substituted by one or more F, NH_2SO_2 and $C_{1-6}alkylSO_2$;
- 20 B^1 is selected from the group consisting of
- 
- and where \bigcirc defines the point of attachment of the ring;
- 25 Q^9 is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, $C_{1-6}alkylOC_{1-6}alkyl$, phenyl, $HO_2CC_{1-6}alkyl$, $C_{1-6}alkylOCOC_{1-6}alkyl$, $C_{1-6}alkylOCO$, $H_2NC_{1-6}alkyl$, $C_{1-6}alkylOCONHC_{1-6}alkyl$ and $C_{1-6}alkylCONHC_{1-6}alkyl$;
- Q^{10} is selected from the group consisting of H and halogen; and
- n is 0 to 4.

Compound of formula (III) may be a compound of formula (IIID)



and pharmaceutically acceptable salts or solvates thereof, wherein all substituents are as for a compound of formula (III) defined hereinabove.

Compound of formula (III) may be a compound of formula (IIIE)

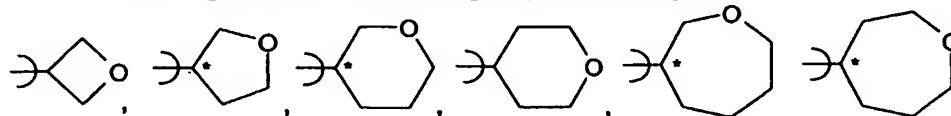



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and pharmaceutically acceptable salts or solvates thereof, wherein

- | | | |
|----|---|--|
| 10 | X
Y
Q ¹ | is selected from the group consisting of oxygen or NQ ² ;
is selected from the group consisting of CH or nitrogen;
is selected from the group consisting of H, C ₁₋₆ alkyl, C ₁₋₂ alkyl substituted by one to five fluorine atoms, C ₁₋₃ alkylOC ₁₋₃ alkyl, C ₃₋₆ alkenyl, C ₃₋₆ alkynyl, C ₃₋₁₀ cycloalkylC ₀₋₆ alkyl, C ₄₋₇ cycloalkyl substituted by C ₁₋₃ alkyl or C ₁₋₃ alkoxy, C ₄₋₁₂ bridged cycloalkyl, A(CR ⁶ R ⁷) _n and B(CR ⁶ R ⁷) _n ; |
| 15 | Q ²
Q ¹ and Q ² | is selected from the group consisting of H and C ₁₋₆ alkyl; or
together with the nitrogen atom to which they are bound form a 4-8 membered saturated heterocyclic ring or a 5-membered heteroaryl ring heteroaryl ring is unsubstituted or substituted by one R ⁸ ; Q ³ is selected from the group consisting of C ₁₋₅ alkyl and C ₁₋₂ alkyl substituted by one to five fluorine atoms; |
| 20 | Q ⁴
Q ⁵ | is selected from the group consisting of C ₁₋₆ alkyl, NH ₂ and R ⁹ CONH;
is selected from the group consisting of hydrogen, C ₁₋₃ alkyl, C ₁₋₂ alkyl substituted by one to five fluorine atoms, C ₁₋₃ alkylO ₂ C, halogen, cyano, (C ₁₋₃ alkyl) ₂ NCO, C ₁₋₃ alkylS and C ₁₋₃ alkylO ₂ S; |

- Q⁶ and Q⁷ are independently H or C₁₋₆alkyl;
 A¹ is selected from the group consisting of unsubstituted 5- or 6-membered heteroaryl unsubstituted 6-membered aryl, 5- or 6-membered heteroaryl substituted by one or more R⁸; and 6-membered aryl substituted by one or more R⁸;
 Q⁸ is selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted by one more fluorine atoms, C₁₋₆alkoxy, C₁₋₆alkoxy substituted by one or more F, NH₂SO₂ and C₁₋₆alkylSO₂;
 B¹ is a ring selected from the group consisting of



- and where  defines the point of attachment of the ring;
 Q⁹ is selected from the group consisting of H, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, phenyl, HO₂CC₁₋₆alkyl, C₁₋₆alkylOCOC₁₋₆alkyl, C₁₋₆alkylOCO, H₂NC₁₋₆alkyl, C₁₋₆alkylOCONHC₁₋₆alkyl and C₁₋₆alkylCONHC₁₋₆alkyl;
 Q¹⁰ is selected from the group consisting of H and halogen; and
 n is 0 to 4.

In another aspect of the invention Y is carbon.

- In another aspect of the invention Q¹ is selected from the group consisting of, C₁₋₆alkyl, C₃₋₁₀cycloalkylC₀₋₆alkyl, C₅₋₆cycloalkyl substituted by C₁₋₂alkyl or C₁₋₂alkoxy, C₁₋₃alkylOC₁₋₃alkyl and C₁₋₂alkyl substituted by one to five fluorine atoms.

Representative examples of Q¹ include cyclohexylmethyl, cyclohexyl, n-butyl, n-pentyl, cyclopentyl, 2-methylpropyl, 2,2-dimethylpropyl, 2,2,2-trifluoroethyl, 2-methoxyethyl and ethyl.

Further representative examples of Q¹ include 1-methylethyl, 1-ethylpropyl, cycloheptyl, cis-4-methylcyclohexyl, trans-4-methylcyclohexyl, cyclobutyl, cyclopentanemethyl, and trans-4-(ethoxy)cyclohexyl.

- In another aspect of the invention Q¹ is selected from the group consisting of A¹(CQ⁶Q⁷)_n and B¹(CQ⁶Q⁷)_n.

Further representative examples of Q¹ include benzyl, 4-chlorobenzyl, 2-furylmethyl, 4-methylphenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-pyridyl, 2-chlorophenyl, 3,5-difluorobenzyl, 3-pyridylmethyl, 2-methylbenzyl, 2-chlorobenzyl, (S)- α -methylbenzyl, (R)- α -methylbenzyl, 6-methylpyridin-3-yl, 4-methoxybenzyl, 4-fluorobenzyl, 2-(5-methylfuryl)methyl, 4-methylbenzyl, 4-pyridylmethyl, 2-pyridylmethyl, 2-(6-methylpyridine)methyl, 2-thiophenylmethyl, 4-pyranylmethyl, 2-tetrahydrofurylmethyl, 2-(5-methylpyrazine)methyl and 4-ethoxybenzyl.

Further representative examples of Q¹ include 1H-imidazol-2-ylmethyl, 1H-pyrazol-4-ylmethyl, (1-methyl-1H-imidazol-2-yl)methyl, (3-methyl-1H-pyrazol-4-yl)methyl, (1-methyl-1H-pyrazol-3-yl)methyl, (1-methyl-1H-pyrazol-4-yl)methyl, (3-methyl-1H-pyrazol-5-yl)methyl, (1-methyl-1H-pyrazol-5-yl)methyl, (1-methyl-1H-1,2,4-triazol-5-yl)methyl, (5-methyl-3-isoxazolyl)methyl, tetrahydro-2H-pyran-4-yl, tetrahydro-2H-pyran-4-ylmethyl, (6-methyl-3-pyridyl)methyl, 2-pyrazinylmethyl, (2-methyl-1H-imidazol-4-yl)methyl, (4-methyl-1H-imidazol-5-yl)methyl, (4-methyl-1H-imidazol-2-yl)methyl, (1-ethyl-1H-imidazol-2-yl)methyl, (1,3-dimethyl-1H-pyrazol-4-yl)methyl, (1,5-dimethyl-1H-pyrazol-4-yl)methyl, (3-methyl-5-isothiazolyl)methyl, (4-methyl-1,3-thiazol-2-yl)methyl, (3-methyl-4-isothiazolyl)methyl, [1-(fluoromethyl)-1H-pyrazol-4-yl]methyl, (2-methyl-3-pyridyl)methyl, (6-methyl-3-pyridyl)methyl, (1-methyl-1H-imidazol-2-yl)methyl, (5-chloro-2-pyridyl)methyl, 1H-imidazol-2-ylmethyl, 4-ethoxyphenyl, 3-chloro-4-methylphenyl, (5-chloro-2-pyridyl)methyl, (6-methyl-3-pyridyl)methyl, 2-methyl-3-pyridyl, 6-methyl-2-pyridyl, 2-pyrazinylmethyl, 2,6-dimethyl-3-pyridyl, 3,4-dichlorobenzyl, 5-chloro-3-pyridyl, 6-chloro-3-pyridazinyl, 3,5-dichlorobenzyl, 2-carboxyphenyl, (5-methyl-2-pyridyl)methyl, 4-chloro-3-(trifluoromethyl)benzyl, (5-bromo-2-pyridyl)methyl, (4-bromo-4-pyridyl)methyl, (3-methyl-4-isoxazolyl)methyl, 5-pyrimidinylmethyl, (3-methyl-1,2,4-oxadiazol-5-yl)methyl, (5-methyl-1,2,4-oxadiazol-3-yl)methyl and (1-ethyl-1H-1,2,4-triazol-5-yl)methyl.

In another aspect of the invention Q¹ is selected from the group consisting of C₃₋₆alkenyl and C₃₋₆alkynyl.

Further representative examples of Q¹ include propargyl and allyl.

In another aspect of the invention Q² is H or C₁₋₂alkyl.

30 Representative examples of Q² include H, methyl and ethyl.

In another aspect of the invention Q³ is CHF₂, CH₂F, CF₃ or C₁₋₄alkyl.

Representative examples of Q³ include CF₃, CH₃ and ethyl.

Further representative examples of Q³ include CH₂F.

In another aspect of the invention Q^4 is C_{1-6} alkyl, such as C_{1-3} alkyl.

Representative examples of Q^4 include CH_3 .

In another aspect of the invention Q^4 is NH_2 .

Further representative examples of Q^4 include NH_2 .

5 In another aspect of the invention Q^5 is hydrogen or C_{1-3} alkyl.

Representative examples of Q^5 include H or CH_3 .

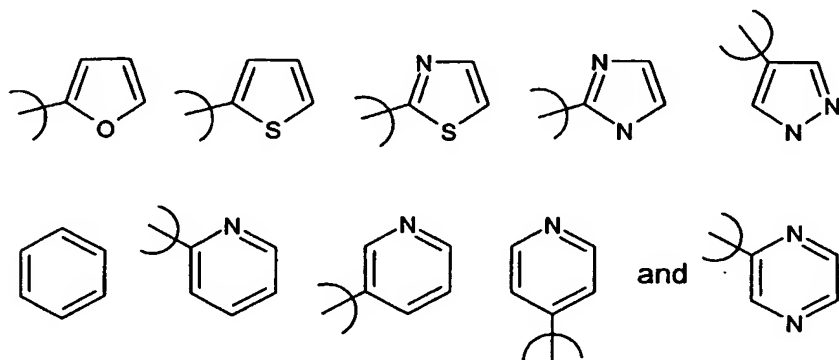
In another aspect of the invention R^5 is CN, halogen or CO_2Et .

Further representative examples of Q^5 include CN, F, Cl, CO_2Et .

In another aspect of the invention Q^6 and Q^7 are independently selected from H or methyl.

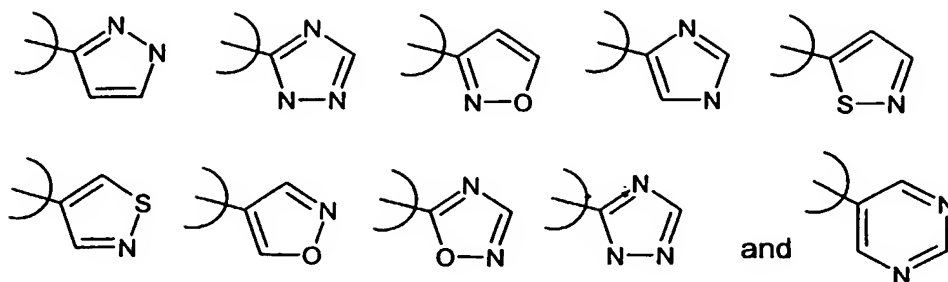
10 In another aspect Q^6 and Q^7 are both H.

In another aspect of the invention A^1 is selected from the group consisting of



where) defines the point of attachment of the ring
and A^1 is unsubstituted or substituted by one or two Q^8 .

In another aspect of the invention A^1 is selected from the group consisting of



where  defines the point of attachment of the ring

In another aspect of the invention Q^8 is selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} alkyl substituted by one to three fluorine atoms (e.g. CF_3), and C_{1-3} alkoxy. Representative examples of Q^8 include F, Cl, CH_3 , methoxy and ethoxy.

- 5 Further representative examples of Q^8 include ethyl, fluoromethyl, CF_3 and Br. Representative examples of B^1 include



In another aspect of the invention Q^9 is selected from the group consisting of C_{1-6} alkyl (e.g. ethyl), phenyl and aminomethyl.

- 10 In another aspect of the invention Q^{10} is H.

In another aspect of the invention in compounds of formula (III), (IIIC) and (IIID) n is 0 to 2 (e.g. 1) or in compounds of formula (IIIE) n is 1 or 2.

In another aspect the invention provides a compound of formula (III) or a pharmaceutically acceptable salt or solvate thereof in which:

- 15 X is oxygen;
 Y is CH;
 Q^1 is $A^1(CR^6R^7)_n$;
 Q^3 is selected from the group consisting of C_{1-5} alkyl and C_{1-2} alkyl substituted by
 one to five fluorine atoms;
 20 Q^4 is C_{1-6} alkyl;
 Q^5 is selected from the group consisting of hydrogen, C_{1-3} alkyl, C_{1-2} alkyl
 substituted by one to five fluorine atoms, C_{1-3} alkyl O_2C , halogen, and C_{1-3} alkylS;
 A^1 is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-
 25 membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl
 substituted by one or more R^8 ;

Q⁸ is selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted by one more fluorine atoms, C₁₋₆alkoxy, and C₁₋₆alkoxy substituted by one or more F;

Q¹⁰ is selected from the group consisting of H and halogen; and

5 n is 0.

Compounds of formula (III) and pharmaceutically acceptable salts and solvates thereof are described in PCT publication No. WO 2004/024691, published 25 March 2004. The disclosures of these references are incorporated herein by reference in their entirety.

10 Compounds of formula (III) may be prepared by any method described in WO 2004/024691 and equivalent patent applications.

In a further embodiment, the present invention provides compounds of formula (III) and pharmaceutically acceptable salts or solvates thereof, for use in the preparation of a
15 medicament for the treatment of schizophrenic disorders as defined above.

In another embodiment, the present invention provides a method for the treatment of schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary
20 acute psychotic disorders comprising administering a therapeutically effective amount of a compound of formula (III) or a pharmaceutically acceptable salts or solvates thereof.

In one embodiment of the present invention provides the use of a compound of formula selected from the following group consisting of:

25 2-(4-fluorophenoxy)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine;
2-(4-methoxyphenoxy)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl)pyrimidine;
2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine;
2-[(5-chloropyridin-3-yl)oxy]-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine;
2-(cyclohexyloxy)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine;
30 3-(4-methylsulfonyl-phenyl)-2-(4-methoxy-phenyl)-pyrazolo[1,5-b]pyridazine;
6-difluoromethoxy-2-(4-fluoro-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]-
pyridazine;
2-(4-ethoxy-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;
2-(4-fluoro-phenyl)-6-methylsulfonyl-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-
35 b]pyridazine;
2-(4-difluoromethoxy-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;
4-[2-(4-ethoxy-phenyl)-pyrazolo[1,5-b]pyridazin-3-yl]-benzenesulfonamide;
6-difluoromethoxy-2-(3-fluoro-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-
b]pyridazine;

- 3-(4-methanesulfonyl-phenyl)-2-(4-methoxy-phenyl)-pyrazolo[1,5-b]pyridazine;
6-difluoromethoxy-2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;
2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;
5 2-(4-fluoro-phenyl)-6-methanesulfonyl-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;
2-(4-difluoromethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;
4-[2-(4-ethoxy-phenyl)-pyrazolo[1,5-b]pyridazin-3-yl]-benzenesulfonamide;
6-difluoromethoxy-2-(3-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine
10 4-ethyl-6-[4-(methylsulfonyl)phenyl]-N-(tetrahydro-2H-pyran-4-ylmethyl)-2-pyridinamine; 4-methyl-N-[(1-methyl-1H-pyrazol-4-yl)methyl]-6-[4-(methylsulfonyl)phenyl]-2-pyridinamine; N-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-methyl-6-[4-(methylsulfonyl)phenyl]-2-pyridinamine;
15 N-[(1,3-dimethyl-1H-pyrazol-4-yl)methyl]-4-methyl-6-[4-(methylsulfonyl)phenyl]-2-pyridinamine;
4-(6-[(1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino)-4-ethyl-2-pyridinyl)benzenesulfonamide;
N-[(1,3-dimethyl-1H-pyrazol-4-yl)methyl]-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-2-pyridinamine;
20 N-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-2-pyridinamine;
4-{4-methyl-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-2-pyridinyl}benzenesulfonamide;
4-methyl-N-[(1-methyl-1H-pyrazol-3-yl)methyl]-6-[4-(methylsulfonyl)phenyl]-2-pyridinamine;
25 N-(cyclohexylmethyl)-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-2-pyridinamine;
N-cyclohexyl-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-2-pyridinamine;
2-[4-(methylsulfonyl)phenyl]-6-[(2-pyridinylmethyl)oxy]-4-(trifluoromethyl)pyridine;
4-methyl-N-[(3-methyl-4-isoxazolyl)methyl]-6-[4-(methylsulfonyl)phenyl]-2-pyridinamine;
30 6-[4-(methylsulfonyl)phenyl]-N-(2-pyridinylmethyl)-4-(trifluoromethyl)-2-pyridinamine;
N-cycloheptyl-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-2-pyridinamine;
N-(cis-4-methylcyclohexyl)-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-2-pyridinamine;
N-(1-ethylpropyl)-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-2-pyridinamine;
N-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-
35 2-pyridinamine;
N-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-2-pyridinamine;
4-methyl-N-[(1-methyl-1H-pyrazol-5-yl)methyl]-6-[4-(methylsulfonyl)phenyl]-2-pyridinamine;

- N-(cyclopentylmethyl)-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-2-pyridinamine;
 N-[(1-ethyl-1H-1,2,4-triazol-5-yl)methyl]-4-methyl-6-[4-(methylsulfonyl)phenyl]-2-
 pyridinamine;
 4-ethyl-6-[4-(methylsulfonyl)phenyl]-2-[(2-pyridinylmethyl)amino]-3-pyridinecarbonitrile;
 5 4-ethyl-2-[(5-methyl-2-pyridinyl)methyl]amino-6-[4-(methylsulfonyl)phenyl]-3-
 pyridinecarbonitrile;
 4-ethyl-2-[(6-methyl-3-pyridinyl)methyl]amino-6-[4-(methylsulfonyl)phenyl]-3-
 pyridinecarbonitrile;
 4-ethyl-2-[(1-methyl-1H-pyrazol-4-yl)methyl]amino-6-[4-(methylsulfonyl)phenyl]-3-
 10 pyridinecarbonitrile;
 4-ethyl-6-[4-(methylsulfonyl)phenyl]-2-[(4-methyl-1,3-thiazol-2-yl)methyl]amino-3-
 pyridinecarbonitrile;
 4-ethyl-6-[4-(methylsulfonyl)phenyl]-2-[(2-pyridinylmethyl)oxy]-3-pyridinecarbonitrile;
 4-ethyl-N-[(1-ethyl-1H-1,2,4-triazol-5-yl)methyl]-6-[4-(methylsulfonyl)phenyl]-2-
 15 pyridinamine;
 4-ethyl-2-[(6-methyl-3-pyridinyl)methyl]oxy-6-[4-(methylsulfonyl)phenyl]-3-
 pyridinecarbonitrile;
 6-[4-(methylsulfonyl)phenyl]-N-[(1-methyl-1H-1,2,4-triazol-5-yl)methyl]-4-(trifluoromethyl)-
 2-pyridinamine;
 20 and pharmaceutically acceptable salts and solvates thereof, for use in the treatment of
 schizophrenic disorders as defined above and the preparation of a medicament for the
 treatment of schizophrenic disorders

- In a particular embodiment of the present invention the compound is selected from the
 25 group consisting of: 2-(4-ethoxy-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]-
 pyridazine; 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine; N-cyclo-
 hexyl-6-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-2-pyridinamine; 2-[4-(methylsulfonyl-
)phenyl]-6-[(2-pyridinylmethyl)oxy]-4-(trifluoromethyl)pyridine; 4-methyl-N-[(1-methyl-1H-
 pyrazol-4-yl)methyl]-6-[4-(methylsulfonyl)phenyl]-2-pyridinamine; 3-(4-methanesulfonyl-
 30 phenyl)-2-(4-methoxy-phenyl)-pyrazolo[1,5-b]pyridazine; 6-difluoromethoxy-2-(4-fluoro-
 phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine; 2-(4-ethoxy-phenyl)-3-(4-
 methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine; 2-(4-difluoromethoxy-
 phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine; 4-[2-(4-ethoxy-phenyl)-
 35 pyrazolo[1,5-b]pyridazin-3-yl]-benzenesulfonamide; 6-difluoromethoxy-2-(3-fluoro-phenyl)-
 3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine; or a pharmaceutically acceptable
 salt or solvate thereof.

Conveniently, compounds of formula (I), (II) and (III) of the invention are isolated following

work-up in the form of the free base. Pharmaceutically acceptable acid addition salts of the compounds of the invention may be prepared using conventional means.

5 It is intended that reference to particular compounds herein be interpreted to mean that the pharmaceutically acceptable salts, solvates and prodrugs of those compounds may also be employed.

10 Typically, a pharmaceutical acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

15 Suitable addition salts are formed from acids which form non-toxic salts and examples are hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, malate, fumarate, lactate, tartrate, citrate, formate, gluconate, succinate, piruvate, oxalate, oxaloacetate, trifluoroacetate, saccharate, benzoate, methansulphonate, ethanesulphonate, benzenesulphonate, p-toluensulphonate, , methanesulphonic, ethanesulphonic, p-toluenesulphonic, and isethionate.

20 In addition, prodrugs are also included within the context of this invention. As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference.

30 Prodrugs are any covalently bonded carriers that release a compound of structure (I), (II) and (III) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or in vivo, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol, sulfhydryl and amine functional groups of the compounds of structure (I), (II) and (III).

40

With regard to stereoisomers, the compounds of structure (I), (II) and (III) may have one or more asymmetric carbon atom and may occur as recemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

5

Furthermore, the invention concerns the use of COX-2 inhibitors of formula (I), (II) and (III) in combination with neuroleptics for the treatment of schizophrenic disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, in particular chronic schizophrenic psychoses and schizoaffective psychoses, temporary acute psychotic disorders.

10

The invention is also directed to a novel kit-of-parts that is suitable for use in the treatment of schizophrenic disorders as above defined, the kit comprising a first dosage form comprising a neuroleptic and a second dosage form comprising a COX-2 inhibitor, for simultaneous, separate or sequential administration.

15

The compounds of formula (I), (II) and (III) and their pharmaceutically acceptable salts and solvates are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

20

The compounds of formula (I), (II) and (III), and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I), (II) and (III), and their pharmaceutically acceptable derivatives.

25

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

30

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a

35

unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

- 5 The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as
10 sparingly soluble derivatives, for example, as a sparingly soluble salt.

As stated above, the compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I), (II) or (III) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

- 15 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or
20 combined pharmaceutical formulations.

- A proposed daily dosage of a compound of formula (I), (II) and (III) for the treatment of man is 0.01mg/kg to 500mg/kg, such as 0.05mg/kg to 100mg/kg, e.g. 0.8-3.0mg/kg, which may be conveniently administered in 1 to 4 doses. The precise dose employed will depend on the age and condition of the patient and on the route of administration. Thus,
25 for example, a daily dose of 0.25mg/kg to 10mg/kg may be suitable for systemic administration.

- In a particular embodiment of the present invention, compounds of formula (I), (II) and (III) are used in the form of tablets for oral administration.

- 30 According to a further embodiment of the present invention, the COX-2 inhibitor of the present invention is used in combination with a neuroleptic drug for the manufacture of a medicament for the treatment of schizophrenic disorders as defined above.

Combinations can also include a mixture of one or more COX-2 inhibitors of the present invention or a mixture of one COX-2 inhibitor of the present invention with another COX-2 inhibitor, for example, available on the market (Celebrex®) or generally known as COX-2 inhibitor with one or more neuroleptic agents, mood stabilisers or antimanic.

5

In a further particular embodiment of the present invention, the combination of a COX-2 inhibitor with a neuroleptic drug is useful for the treatment of schizophrenia.

Both classical and atypical neuroleptics can be used for the add-on use according to the invention, in particular atypical neuroleptics.

10

Examples of neuroleptic drugs that are useful in the present invention include, but are not limited to: butyrophenones, such as haloperidol, pimozide, and droperidol; phenothiazines, such as chlorpromazine, thioridazine, mesoridazine, trifluoperazine, perphenazine, fluphenazine, thiflupromazine, prochlorperazine, and acetophenazine; thioxanthenes, such as thiothixene and chlorprothixene; thienobenzodiazepines; dibenzodiazepines; benzisoxazoles; dibenzothiazepines; imidazolidinones; benzisothiazolyl-piperazines; triazine such as lamotrigine; dibenzoxazepines, such as loxapine; dihydroindolones, such as molindone; aripiprazole; and derivatives thereof that have antipsychotic activity.

15

20

Examples of neuroleptic drugs that may be selected for use in the present invention are shown in Table 1.

Table 1
Neuroleptic drugs

25

Common Name	Trade Name	Route of Administration	Form	Dosage Range and (Median) ^a
Clozapine	CLOZARIL	oral	tablets	12.5-900 mg/day (300-900 mg/day)
Olanzapine	ZYPREXA	oral	tablets	5-25 mg/day (10-25 mg/day)
Ziprasidone	GEODON	oral	capsules	20-80mg/twice a day (80-160 mg/day)
Risperidone	RISPERDAL	oral	solution tablets	2-16 mg/day

				tablets (4-12 mg/day)
Quetiapine fumarate	SEROQUEL	oral	tablets	50-900 mg/day (300-900 mg/day)
Sertindole	SERLECT			(4-24 mg/day)
Amisulpride				
Haloperidol	HALDOL	oral	tablets	1-100 mg/day (1-15 mg/day)
Haloperidol Decanoate	HALDOL Decanoate	parenteral	injection	
Haloperidol lactate	HALDOL INTENSOL	oral	solution	
		parenteral	injection	
Chlorpromazine	THORAZINE	rectal	suppositories	30-800 mg/day (200-500 mg/day)
		oral	capsules solution tablets	
		parenteral	injection	
Fluphenazine	PROLIXIN			0.5-40 mg/day (1-5 mg/day)
Fluphenazine decanoate	PROLIXIN Decanoate	parenteral	injection	(about one-half the dosage shown for oral)
Fluphenazine enanthate	PROLIXIN	parenteral	injection	(same as above)
Fluphenazine hydrochloride	PROLIXIN	oral	elixir solution	
		parenteral	injection	
Thiothixene	NAVANE	oral	capsules	6-60 mg/day (8-30 mg/day)
Thiothixene hydrochloride	NAVANE	oral	solution	
		parenteral	injection	
Trifluoperazine	STELAZINE			(2-40 mg/day)

Perphenazine	TRILAFON	oral	solution tablets	12-64 mg/day (16-64 mg/day)
		parenteral	injection	
Perphenazine and Amitriptyline hydrochloride	ETRAFON TRIAVIL	oral	tablets	
Thioridazine	MELLARIL	oral	suspension solution tablets	150-800 mg/day (100-300 mg/day)
Mesoridazine				(30-400 mg/day)
Molindone	MOBAN			50-225 mg/day (15-150 mg/day)
Molindone hydrochloride	MOBAN	oral	solution	
Loxapine	LOXITANE			20-250 mg/day (60-100 mg/day)
Loxapine hydrochloride	LOXITANE	oral	solution	
		parenteral	injection	
Loxapine succinate	LOXITANE	oral	capsules	
Pimozide				(1-10 mg/day)
Flupenthixol				
Promazine	SPARINE			
Trifluorpromazine	VESPRIN			
Chlorprothixene	TARACTAN			
Droperidol	INAPSINE			
Acetophenazine	TINDAL			
Prochlorperazine	COMPAZINE			
Methotrimeprazine	NOZINAN			
Pipotiazine	PIPOTRIL			
Aripiprazole				
Hoperidone				

Examples of tradenames and suppliers of selected neuroleptic drugs are as follows :
 clozapine (available under the tradename CLOZARIL®, from Mylan, Zenith Goldline,
 UDL, Novartis); olanzapine (available under the tradename ZYPREX®, from Lilly ;
 ziprasidone (available under the tradename GEODON®, from Pfizer); risperidone
 5 (available under the tradename RISPERDAL®, from Janssen); quetiapine fumarate
 (available under the tradename SEROQUEL®, from AstraZeneca); haloperidol (available
 under the tradename HALDOL®, from Ortho-McNeil); chlorpromazine (available under the
 tradename THORAZINE®, from SmithKline Beecham (GSK); fluphenazine (available
 under the tradename PROLIXIN®, from Apothecon, Copley, Schering, Teva, and
 10 American Pharmaceutical Partners, Pasadena); thiothixene (available under the
 tradename NAVANE®, from Pfizer); trifluoperazine (10-[3-(4-methyl-1-piperazinyl)propyl]-
 2-(trifluoromethyl)phenothiazine dihydrochloride, available under the tradename
 STELAZINE®, from Smith Klein Beckman; perphenazine (available under the tradename
 TRILAFON®, from Schering); thioridazine (available under the tradename MELLARIL®;
 15 from Novartis, Roxane, HiTech, Teva, and Alpha) ; molindone (available under the
 tradename MOBAN®, from Endo); and loxapine (available under the tradename
 LOXITANE®, from Watson). Furthermore, benperidol (Glianimon®), perazine (Taxilan®)
 or melperone (Eunerpan®) may be used.

20 Other available neuroleptic drugs include promazine (available under the tradename
 SPARINE®), triflurpromazine (available under the tradename VESPRIN®),
 chlorprothixene (available under the tradename TARACTAN®), droperidol (available
 under the tradename INAPSINE®), acetophenazine (available under the tradename
 TINDAL®), prochlorperazine (available under the tradename COMPAZINE®),
 25 methotrimeprazine (available under the tradename NOZINAN®), pipotiazine (available
 under the tradename PIPOTRIL®), ziprasidone, and hoperidone.

Other neuroleptic drugs include the compounds disclosed in the patent application
 WO03/099786, filed by the same Applicant of the present invention. Among them the
 30 compound 7-[4-(4-chloro-benzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-
 tetrahydro-1H-3-benzazepine and its pharmaceutically acceptable salts are particularly
 preferred.

35 In a further particular embodiment of the present invention neuroleptic drugs include
 risperidone and aripiprazole (from Bristol Myers Squibb Company, see e. g. Stahl SM;
 Dopamine-system stabilizers, aripiprazole and the next generation of antipsychotics, part
 1,"goldilocks"-actions at dopamine receptors; J. Clin. Psychiatry 2001,62,11: 841-842).

In a special embodiment of the present invention the neuroleptic drug within the present invention is risperidone (Risperdal®), its manufacture and pharmacological activity is described in EP 0 196 132. Risperidone acts as an antagonist to neurotransmitters, in particular dopamine, and is used for the treatment of psychoses.

Within the present invention, the neuroleptic risperidone can be administered at a dose of 2-6 mg/day, preferably 4-5 mg. The dose for compounds (I) may range from 0.25 mg/kg to 5 mg/kg, preferably 0.8 mg/kg to 3.0 mg/kg. Preferably, the administration occurs once daily.

Various types of mood stabilisers can be used for the add-on use according to the present invention. Examples of mood stabilisers that are useful in the present invention include, but are not limited to: lithium, valproate, carbamazepine, gabapentin, topiramate, oxcarbazepine, lamotrigine. Lithium in particular may be selected.

The invention is also directed to a novel kit-of-parts that is suitable for use in the treatment of schizophrenic disorders such as schizophrenia, delusional disorders, affective disorders, autism or tic disorders, comprising a first dosage form comprising a neuroleptic agent and a second dosage form comprising the COX-2 inhibitor as defined in the present invention or prodrug thereof, for simultaneous, separate or sequential administration.

According to a further particular embodiment, the dosage form comprising a neuroleptic agent and the second dosage form comprising the COX-2 inhibitor as defined in the present invention are administered simultaneously.

The subject pharmaceutical kit-of-parts may be administered enterally (orally) or parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. In a further particular embodiment of the present invention the administration of a pharmaceutical kit comprising the COX-2 inhibitor as defined in the present invention and a neuroleptic occurs enterally (orally), in form of tablets.

The treatment of schizophrenic disorders with the COX-2 inhibitor as defined in the present invention, alone or in combination with a neuroleptic, may occur in addition to further drug therapies.

Thus, tranquilizers may be used for the treatment of agitation, anxiety or sleep disturbances. Preferably lorazepam is used, which belongs to the class of benzodiazepines.

5 EXPERIMENTAL PART

The Intermediates and Examples that follow illustrate the invention but do not limit the invention in any way. All temperatures are in °C. Flash column chromatography was carried out using Merck 9385 silica. Solid Phase Extraction (SPE) chromatography was carried out using Varian Mega Bond Elut (Si) cartridges (Anachem) under 15mmHg vacuum. Thin layer chromatography (Tlc) was carried out on silica plates. In addition to those already defined, the following abbreviations are used: Me, methyl; Ac, acyl; DMSO, dimethylsulphoxide; TFA, trifluoroacetic acid; DME, dimethoxyethane; DCM, dichloromethane; NMP, N-methyl pyrrolidone; and MTBE, methyl t-butyl ether.

15 EXAMPLE 1

Preparation of compounds of formula (I)

Compounds of formula (I) may be prepared by any method described in WO 02/096885, US Appl. Serial N° 10/477547 and equivalent patent applications.

20 Intermediate 1

4,4,4-Trifluoro-1-[4-(methylthio)phenyl]butane-1,3-dione

To a solution of ethyl trifluoroacetate (7.95ml, 1.1eq) in MTBE (125ml) was added dropwise 25% sodium methoxide in methanol (16ml, 1.2eq). 4-Methylthioacetophenone (Aldrich, 10g, 0.06mol) was added portionwise and the mixture stirred at ambient temperature overnight. 2N Hydrochloric acid (40ml) was added cautiously and the organic phase separated, washed with brine and dried (Na₂SO₄) to give an orange solid. The orange solid was recrystallised from hot isopropanol to give the title compound as a yellow crystalline solid (11.25g, 71%).

30 MH- 261

Intermediate 2

2-(Methylthio)-4-[4-(methylthio)phenyl]-6-(trifluoromethyl) pyrimidine

To a mixture of 4,4,4-trifluoro-1-[4-(methylthio)phenyl]butane-1,3-dione (5g) and 2-methyl-2-thiopseudourea sulfate (5.1g, 0.98eq) in acetic acid (100ml) was added sodium acetate (3g, 2eq) and heated under reflux for 8h. The mixture was concentrated *in vacuo* and water (100ml) added to give a solid, which was isolated by filtration to give the title compound as a yellow solid (5.8g, quantitative).

35 MH+ 317

Intermediate 32-(Methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine

- 5 To a solution of 2-(methylthio)-4-[4-(methylthio)phenyl]-6-(trifluoromethyl) pyrimidine (5.78g) in MeOH (500ml) was added a solution of OXONE™ (Aldrich, 56.23g, 5eq) in water (200ml). The mixture was stirred at ambient temperature overnight, concentrated *in vacuo* and the residue partitioned between water and ethyl acetate (2 x 100ml). The combined organic phases were dried and concentrated *in vacuo* to an off-white solid which was triturated with hot isopropanol to give the title compound as a white solid (5.6g, 80%).
- 10

MH+ 381

Tlc SiO₂ Ethyl acetate:cyclohexane (1:1) R_f 0.45Example 1.1

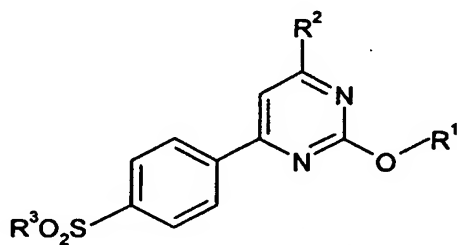
- 15 2-(4-Fluorophenoxy)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine.

- To a stirred solution of 4-fluorophenol (37mg, 0.33mmole) in dry tetrahydrofuran (10ml) was added, under an atmosphere of nitrogen, sodium hydride (60% dispersion in oil, 13mg, 0.33mmole) and the resulting mixture stirred at 20 for 30min. To the stirred reaction mixture was added 2-(methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl)pyrimidine (114mg, 0.33mmole) in a single portion, and stirring was continued for 2h. The solvent was evaporated, and the residue partitioned between dichloromethane and 2N sodium hydroxide. The dried organic phase was evaporated to dryness. The residue was purified on a silica gel SPE cartridge eluting with chloroform to afford the title compound as a colourless solid (99mg, 80%).
- 20

- 25 MH+ 413.

Examples 1.2 to 1.10

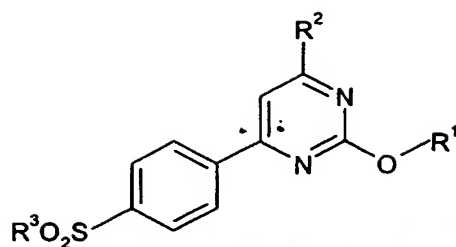
Examples 1.2 to 1.10, as shown in Table 1 that follows, were prepared in the manner described for Example 1.1

Table 1

(I)

Ex	R ¹	R ²	R ³	MS
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Table 1



Ex	R ¹	R ²	R ³	MS
1.2	3,4-difluorophenyl	CF ₃	CH ₃	MH ⁺ 431
1.3	4-methoxyphenyl	CF ₃	CH ₃	MH ⁺ 425
1.4	4-fluorobenzyl	CF ₃	CH ₃	MH ⁺ 427
1.5	4-bromophenyl	CF ₃	CH ₃	MH ⁺ 474
1.6	4-methylphenyl	CF ₃	CH ₃	MH ⁺ 409
1.7	5-chloropyridin-3-yl	CF ₃	CH ₃	MH ⁺ 431
1.8	cyclohexyl	CF ₃	CH ₃	MH ⁺ 401
1.9	cyclopentylmethyl	CF ₃	CH ₃	MH ⁺ 401
1.10	n-butyl	CF ₃	CH ₃	MH ⁺ 375

Example 1.11**2-Butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine**

- 5 Sodium methoxide (6.6kg of a 30%w/w solution in methanol) was added over at least 30min to a solution of 4-(methylthio)acetophenone (5.0kg) and methyl trifluoroacetate (4.25kg) in tert-butylmethylether (40L) at 40±3°C. The solution was heated at 40±3°C for at least 3h. Acetic acid (55L) was added, followed by S-methyl 2-thiopseudourea sulfate (5.45kg) and the mixture concentrated to ca. 45L. The mixture was heated at about 110°C for at least a further 8h (overnight) then acetic acid (20L) was added before cooling to 50±3°C. A solution of sodium tungstate dihydrate (0.2kg) in water (2.5L) was added, followed by hydrogen peroxide (20.7kg of 30%w/v solution), which was added over at least 3h, maintaining the temp at ca. 50°. The mixture is heated at ca. 50°C for at least 12h before cooling to 20±3°C. A solution of sodium sulphite (3.45kg) in water (28L) was then added over at least 30min whilst maintaining the temperature at 20±3°. The mixture was aged at 20±3°C for ca. 1h and 2-(methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-
- 10
- 15

(trifluoromethyl)pyrimidine collected by filtration, washed with water (3x15L) and dried at up to 60° *in vacuo*. Yield, 9.96kg, 90% of theory.

A suspension of 2-(methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-pyrimidine (525g) in n-butanol (5.25L) was treated with potassium carbonate (210g) at 20±5°C. The mixture was heated to 50±5°C overnight until the reaction was complete by HPLC. Acetic acid (1.57L) was added dropwise, to control any gas evolution, keeping the temperature at 50±5°C. Water (3.67L) was then added over 30min keeping the temperature at 50±5°C to allow full crystallisation to occur. The slurry was then cooled to 20-25°C and aged for at least 1 hour. The resulting product was then filtered under vacuum and washed with a mixture of n-butanol (787mL), acetic acid (236mL), and water (551mL) followed by water (2x1.57L). The product was then dried at up to ca50°C under vacuum to yield the title compound. Yield, 457g, 88.4% of theory. The title compound was found to be identical to that of Example 10.

¹H NMR (CDCl₃) δ: 8.33(2H, d, para-di-substituted CH); 8.11(2H, d, para-di-substituted CH); 7.70(1H, s, aromatic CH); 4.54(2H, t, butyl CH₂); 3.12(3H, s, sulphone CH₃); 1.88(2H, m, butyl CH₂); 1.55(2H, m, butyl CH₂); 1.01(3H, t, butyl CH₃).

EXAMPLE 2

Preparation of compounds of formula (II)

Compounds of formula (II) may be prepared by any method described in WO 99/12930, US Patent N° 6,451,794, US-A-2003-0040517 and US-A-2003-0008872 and equivalent patent applications.

Example 2.1

6-Difluoromethoxy-2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine

(i) 6-Methoxy-2-(4-fluoro-phenyl-pyrazolo[1,5-b]pyridazine-3-carboxylic acid methyl ester. 1,8-Diazabicyclo[5.4.0]undec-7-ene (3.39mL) was added to a mixture of 3-(4-fluorophenyl)-prop-2-ynoic acid methyl ester (3.36g) and 1-amino-3-methoxy-pyridazin-1-ium mesitylene sulphonate¹ (6.1419g) in acetonitrile (125mL) and the mixture was stirred at ambient temperature for 48 hours. During the first 2 hours a stream of air was passed through the reaction. The mixture was concentrated *in vacuo*, dissolved in ethyl acetate (150mL), washed with water (3 x 25mL), dried (MgSO₄), filtered and evaporated *in vacuo* to give the title compound as a brown solid (4.77g).

¹H NMR (CDCl₃): 8.4 (d, 1H, J=10Hz) 7.85-7.90 (m, 2H) 7.1-7.2 (m, 2H) 6.9-7.0 (d, 1H, J=10Hz) 4.1 (s, 3H) 3.9 (s, 3H)

MH⁺ 302

Ref.¹ T. Tsuchiya, J. Kurita and K. Takayama, Chem. Pharm. Bull. 28(9) 2676-2681 (1980).

(ii) 6-Methoxy-2-(4-fluoro-phenyl-pyrazolo[1,5-b]pyridazine-3-carboxylic acid

A mixture of 6-methoxy-2-(4-fluoro-phenyl-pyrazolo[1,5-b]pyridazine-3-carboxylic acid methyl ester (4.469g), 2N sodium hydroxide (50mL) and methanol (90mL) was heated at reflux for 2 hours. The cooled solution was added to 2N hydrochloric acid (200mL) and the title compound was isolated by filtration as a beige solid (3.639g).

¹H NMR (DMSO-d₆): 12.8 (br. s, 1H) 8.4 (d, 1H, J=10Hz) 7.8-7.9 (m, 2H) 7.21-7.32 (m, 2H) 7.15-7.2 (d, 1H, J=10Hz) 4.0 (s, 3H)

MH⁺ 288

(iii) 2-(4-Fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-6-methoxy-pyrazolo[1,5-b]-pyridazine

A mixture of 6-methoxy-2-(4-fluoro-phenyl-pyrazolo[1,5-b]pyridazine-3-carboxylic acid (869mg) and sodium bicarbonate (756mg) in dimethylformamide (10mL) was treated with N-bromosuccinimide (587mg) and stirred at ambient temperature for 1 hour, then added to water (50mL) and extracted with ethyl acetate (3x50mL), dried (MgSO₄), and evaporated *in vacuo*. The resulting brown solid (1.612g) was dissolved in 1,2 dimethoxyethane (20mL). 2N Aqueous sodium carbonate solution (10mL) was added together with 4-(methanesulphonyl)phenyl boronic acid (660mg) and tetrakis(triphenylphosphine)palladium (0) (100mg) and the mixture was heated at reflux for 20 hours. The reaction was poured into water(50mL), extracted with dichloromethane (3x100mL). The combined organic extracts were dried (MgSO₄) and evaporated *in vacuo* to give a brown solid (1.116g) which was purified by flash column chromatography on silica, eluting with cyclohexane/ethyl acetate (4:1 then 2:1), to give the title compound as a yellow solid (390mg).

Tlc, SiO₂, R_f 0.3 (1:1 cyclohexane/ethyl acetate), detection UV

MH⁺ 398

(iv) 2-(4-Fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazin-6-ol

A mixture of 2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-6-methoxy-pyrazolo[1,5-b]pyridazine (321mg) and pyridine hydrochloride (1.4g) was heated to and at 200°C in a sealed vessel (ReactivialTM) for 3 hours. The cooled reaction was poured into water (20mL), and extracted with ethyl acetate (3x30mL). The combined organic extracts dried (MgSO₄), filtered and evaporated *in vacuo* to give a solid which was triturated with diethyl ether to give the title compound as a beige solid (119mg).

Tlc, SiO₂, Rf 0.07 (1:2 cyclohexane/ethyl acetate), detection UV.
MH⁺ 384

(v) 6-Difluoromethoxy-2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine

A solution of 2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazin-6-ol (0.2 g) in anhydrous dimethyl formamide (5 mL) was treated with sodium hydride (0.046g, 60% dispersion in mineral oil), after effervescence ceased a stream of bromodifluoromethane gas was passed through the mixture at ambient temperature for 30 minutes. The reaction mixture was then poured into water (50 mL) and extracted with ethyl acetate (50 mL), the organic extract was washed with water (3X 50 mL), dried and concentrated *in vacuo*. The residue was purified by chromatography to give the title compound as a white solid (0.17g).

MH⁺ = 434

¹H NMR(CDCl₃): δ 8.05-8.0(d, J=10HZ, 2H) 8.0-7.95(d, J=10HZ, 1H) 7.6-7.5(m, 4H) 7.8-7.2(t, J=70HZ, 1H) 7.1-7.05(t, J=11HZ, 2H) 6.9-6.85(d, J=10HZ, 1H) 3.15(s, 3H)

Tlc, SiO₂, Rf 0.35(ethyl acetate/cyclohexane(1/1))

Example 2.2

3-(4-Methanesulfonyl-phenyl)-2-(4-methoxy-phenyl)-pyrazolo[1,5-b]pyridazine

(i) 2-(4-Methoxy-phenyl)-pyrazolo[1,5-b]pyridazine-3-carboxylic acid methyl ester

Diazabicyclo[5.4.0]undec-7-ene (22.76mL, 2eq) was added dropwise to a solution of methyl 3-(4-methoxy-phenyl)-prop-2-ynoic acid¹ (14.46g, 76mM) and 1-amino pyridazinium iodide² (2eq) in acetonitrile under nitrogen and stirred for 6h. Purification by chromatography on silica gel eluting with toluene, then toluene:ethyl acetate (9:1) gave the title compound (2.76g) as a brown solid.

MH⁺ 284

¹H NMR (CDCl₃) δ 3.87 (3H, s) 3.9 (3H, s) 7.0 (2H, d, J=9Hz) 7.25 (1H, dd, J= 9 & 4Hz) 7.90 (2H, d, J = 9Hz) 8.45 (1H, dd, J=4 & 2Hz) 8.55 (1H, dd, J=9 & 2 Hz)

Ref: ¹ J.Morris and D.G.Wishka, Synthesis (1994), (1), 43-6

Ref: ² Kobayashi *et al* Chem.Pharm.Bull. (1971), 19 (10), 2106-15

(ii) 3-(4-Methanesulfonyl-phenyl)-2-(4-methoxy-phenyl)-pyrazolo[1,5-b]pyridazine

A mixture of 2-(4-methoxy-phenyl)-pyrazolo[1,5-b]pyridazine-3-carboxylic acid methyl ester (2.76g) and aq. sodium hydroxide (2N, 30mL) in ethanol (30mL) was refluxed under nitrogen for 2h. The cooled mixture was acidified with hydrochloric acid (2N) and the resulting white solid (2.53g) isolated by filtration. This solid was dissolved in DMF and sodium bicarbonate (2.67g, 3.3eq) added, followed by N-bromosuccinimide (1.88g, 1.1eq) portionwise. After stirring for 1h under nitrogen, water was added and extracted into ethyl acetate (2x 25mL). The dried organic phase was concentrated and the residue taken up

in DME (60mL). Aqueous sodium carbonate (2N, 15mL) was added, followed by 4-methanesulfonyl-phenylboronic acid (3.12g) and tetrakis(triphenylphosphine)palladium(0) (250mg). The mixture was heated at reflux under nitrogen for 18h, cooled, poured into water and extracted into ethyl acetate (2 x 25mL). The combined organic phases were dried and concentrated onto silica gel. Chromatography on silica gel eluting with toluene:ethyl acetate (8:1) gave, on concentration, the title compound (3.58g) as a cream solid.

MH⁺ 380

¹H NMR (DMSO) δ 3.25 (3H, s) 3.75 (3H, s) 6.95 (2H, d, J= 8.5 Hz) 7.25 (1H, dd, J = 9 & 5Hz) 7.45 (2H, d, J= 8.5Hz) 7.60 (2H, d, J= 8Hz) 7.9 (2H, d, J= 8.5 Hz) 8.15 (1H, dd, J = 9&2Hz) 8.49 (1H, dd, J= 5&2Hz)

Example 2.3

2-(4-Ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine

(i) 4-[3-(4-Methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazin-2-yl]-phenol

Boron tribromide (1M solution in CH₂Cl₂, 2.1 eq) was added to 3-(4-methanesulfonyl-phenyl)-2-(4-methoxy-phenyl)-pyrazolo[1,5-b]pyridazine (3.58g) in CH₂Cl₂ at -70°. The mixture was stirred for 10min then warmed to 0° and stirred at 0° overnight. The reaction mixture was made alkaline with potassium carbonate then acidified with hydrochloric acid (2M), poured into water and extracted into CH₂Cl₂. The organic phase was dried, filtered and concentrated to give the title compound (1.87g) as a yellow solid.

MH⁺ 366

¹H NMR (DMSO) δ 3.30 (3H, s) 6.80 (2H, d, J= 8.5 Hz) 7.30 (1H, dd, J = 9 & 5Hz) 7.35 (2H, d, J= 8.5Hz) 7.60 (2H, d, J= 8Hz) 8.0 (2H, d, J= 8.5 Hz) 8.20 (1H, dd, J = 9& 2Hz) 8.55 (1H, dd, J = 5& 2Hz) 9.75 (1H, s)

(ii) 2-(4-Ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine

4-[3-(4-Methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazin-2-yl]-phenol (663mg, 1.82), iodoethane (1eq) and potassium carbonate (2eq) in acetonitrile (30mL) were heated at reflux under nitrogen for 18h. The cooled reaction mixture was partitioned between water (30mL) and ethyl acetate (30 mL). The organic phase was collected, dried and purified by chromatography to give the title compound (547mg) as a cream foam.

MH⁺ 394

¹H NMR (DMSO) δ 1.45 (3H, t, J=7Hz) 3.10 (3H, s) 4.1 (2H, q, J=7Hz) 6.87 (2H, d, J= 9 Hz) 7.08 (1H, dd, J = 9 & 5Hz) 7.55 (4H, t, J= 9Hz) 7.92 (1H, dd, J= 9 & 2 Hz) 7.95 (2H, d, J= 9 Hz) 8.20 (1H, dd, J = 9& 2Hz) 8.32 (1H, dd, J = 5& 2Hz)

Example 2.4

2-(4-Fluoro-phenyl)-6-methanesulfonyl-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine

(i) 2-(4-Fluoro-phenyl)-6-methylsulfanyl-pyrazolo[1,5-b]pyridazine-3-carboxylic acid methyl ester

- 5 Solid t-butoxycarbonyl-O-mesitylenesulfonylhydroxylamine¹ (7.8g) was added portionwise with stirring to TFA (25mL) over 10min then stirred for a further 20 minutes. The solution was poured onto ice (~200mL) and left until the ice melted. The resulting white solid was filtered off, washed with water, and dissolved in DME (100mL). The solution was dried over 4A mol. sieves for 1.5 hours, filtered then added to a solution of 3-methylthio-pyridazine² (2.6g) in dichloromethane (35mL) and the reaction stirred at room temperature for 20h. The intermediate salt was isolated by filtration as light brown crystals (3.87g), suspended in acetonitrile (100mL) and methyl 3-(4-fluoro-phenyl)-prop-2-ynoic acid (2.02g) added. 1,8-Diazabicyclo[5.4.0]undec-7-ene (2.1mL) was added dropwise and the reaction was stirred at room temperature for 20 hours. The resulting crystalline precipitate was filtered off, washed and dried (770mg). Concentration of the filtrate gave a second crop (430mg). The residues were partitioned between water and ethyl acetate (100mL each) and the aqueous layer was extracted with ethyl acetate (20mL). The combined organics were washed with water, brine and dried. Removal of solvent gave a brown oil which was purified by flash chromatography on silica (300g) eluting with cyclohexane / ethyl acetate (3:1) to give a further quantity of product (247mg). The three crops were combined to give the title compound (1.45g) as a light brown solid.

MH⁺ 318

¹H NMR (CDCl₃) δ 2.70 (3H, s), 3.88 (3H, s) 7.08-7.18 (3H, m) 7.84 (2H, m) 8.31 (1H, d, J = 10Hz)

- 25 Ref: ¹ K Novitskii *et al*, Khim Geterotskil Soedin, 1970 2, 57-62

Ref: ² Barlin G. B., Brown, W. V., J Chem Soc (1968), (12), 1435-45

(ii) 2-(4-Fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-6-methylsulfanyl-pyrazolo[1,5-b]pyridazine

- 30 A mixture of the 2-(4-fluoro-phenyl)-6-(methylthio)-pyrazolo[1,5-b]pyridazine-3-carboxylic acid methyl ester (1.45g) potassium carbonate (690mg) in methanol (40mL) and water (14mL) was stirred and heated under reflux for 20 hours under nitrogen. The solvents were removed and the resulting solid partitioned between ethyl acetate (50mL) and water (250mL). The aqueous layer was acidified to pH1 (2M HCl) and a solid was filtered off (1.0g, MH⁺ 304). A mixture of the solid (1.0g), sodium bicarbonate (557mg) and NBS (594mg) were stirred at room temperature for 4 hours. The reaction was poured into water (150mL) and extracted with ethyl acetate (3x50mL). The combined extracts were washed with water (50mL), brine (20mL), dried and concentrated. The resulting solid (1.015g, MH⁺ 338,340), 4-(methanesulphonyl)phenyl boronic acid (902mg), sodium carbonate (740mg) and tetrakis(triphenylphosphine)palladium(0) (175mg) were stirred

and heated under nitrogen at reflux in DME (30mLs) and water (15mL) for 48 hours. The reaction was poured into water and extracted with ethyl acetate (3x50mL). The combined extracts were dried and the solvent removed to give a brown solid. This was purified on silica (300g) eluting with cyclohexane, ethyl acetate (1:1) to give the title compound (0.713g) as a yellow solid.

MH⁺ 414

¹H NMR δ (DMSO) 2.65 (3H, s) 3.28 (3H, s) 7.20 -7.30 (3H, m) 7.55 (2H, m) 7.62 (4H, d, J = 8.5Hz) 7.95-8.05 (3H, m)

(iii) 2-(4-Fluoro-phenyl)-6-methanesulfonyl-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine

A suspension of 2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-6-(methylthio)-pyrazolo[1,5-b]pyridazine (60mg 0.145) in MeOH (5mL) and water (2mL) was stirred with oxone (196mg 0.32) for 20 hours. The resulting solution was poured into water (50mL) and extracted with chloroform (3x20mL). The combined extracts were dried and the solvent removed. Crystallisation of the residue from methanol gave the title compound (60mg) as a white solid.

MH⁺ 446

¹H NMR (DMSO-d₆) δ 3.34 (3H, s) 3.53 (3H, s) 7.33 (2H, t, J = 9Hz) 7.62 (2H, m) 7.68 (1H, d, J = 8.5Hz) 8.04 (1H, d, J = 10Hz) 8.52 (1H, d, J = 9Hz)

TLC SiO₂ Hexane:Ethyl acetate (1:1) R_f 0.24 UV

Example 2.5

2-(4-Difluoromethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine

Sodium hydride (48mg, 60% disp. in oil, 1.2mmol) was added to a solution of 4-[3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazin-2-yl]-phenol (200mg, 0.55mmol) in anhydrous dimethylformamide (5mL). Bromodifluoromethane gas was gently bubbled through the solution for 20min, then diluted with CH₂Cl₂ (30mL). Aqueous workup followed by chromatography on silica gel with CH₂Cl₂:ethyl acetate (3:1) as eluant then chromatography with CH₂Cl₂:ethyl acetate (10:1) as eluant gave the title compound (63mg, 28%) as a white solid.

MH⁺ 416

NMR (CDCl₃) δ 8.38 (1H, dd, J=4Hz), 8.01 (2H, d, J = 8.5Hz), 7.94 (1H, dd, J= 9 & 2Hz), 7.65 (2H, d, J 8.5 Hz) 7.57 (2H, d, J = 8Hz), 7.10 (3H, m), 6.87 - 6.27 (1H, t, J= 7.4Hz) 3.15 (3H, s)

Example 2.6

4-[2-(4-Ethoxy-phenyl)-pyrazolo[1,5-b]pyridazin-3-yl]-benzenesulfonamide

(i) 2-(4-Ethoxy-phenyl)-pyrazolo[1,5-b]pyridazine-3-carboxylic acid methyl ester

Diazabicyclo[5.4.0]undec-7-ene (1.47mL, 2eq) was added dropwise to a solution of methyl 3-(4-ethoxy-phenyl)-prop-2-ynoic acid (1.0g) and 1-amino pyridazinium iodide² (2.19g) in acetonitrile (10mL) under nitrogen and stirred for 5h. Concentration and aqueous workup gave the title compound (1.2g) as a sticky brown solid.

5 MH⁺ 298

(ii) 2-(4-Ethoxy-phenyl)-pyrazolo[1,5-b]pyridazine-3-carboxylic acid

A mixture of 2-(4-ethoxy-phenyl)-pyrazolo[1,5-b]pyridazine-3-carboxylic acid methyl ester (1.2g), ethanol (10mL) and 2N sodium hydroxide (10mL) was heated to 80° for 1.5h. The mixture was allowed to cool and acidified to pH 1 with 2N hydrochloric acid. The title compound was isolated by filtration as a brown solid (716mg, 63%).

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MH⁺ 284

(iii) 2-(4-Ethoxy-phenyl)-3-iodo-pyrazolo[1,5-b]pyridazine

A mixture of 2-(4-ethoxy-phenyl)-pyrazolo[1,5-b]pyridazine-3-carboxylic acid (710mg), N-iodosuccinimide (678mg) and sodium bicarbonate (717mg) in DMF (8mL) was stirred for 4h. A further quantity of N-iodosuccinimide(100mg) was added and stirring continued for 2h. Aqueous workup gave a dark brown solid which was purified by SPE with dichloromethane as eluant. This gave the title compound as an orange-brown solid (429mg, 47%).

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MH⁺ 366

(iv) 4-[2-(4-Ethoxy-phenyl)-pyrazolo[1,5-b]pyridazin-3-yl]-benzenesulfonamide

A mixture of 4-iodobenzenesulphonamide (0.311g), dipinacoldiborane¹ (0.279g), potassium acetate (486mg) and [1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) chloride complex with dichloromethane (1:1) (0.45g) in dimethylformamide (8mL) was heated under nitrogen at 80° for 2 h. The cooled reaction mixture was concentrated *in vacuo* and the residue suspended in 1,2 dimethoxyethane (10 mL), 2-(4-ethoxy-phenyl)-3-iodo-pyrazolo[1,5-b]pyridazine (0.4g) was added together with 2N sodium carbonate (4mL) and tetrakis(triphenylphosphine)palladium (0) (20mg) and the mixture heated at reflux under nitrogen for 18 hours. The cooled reaction mixture was poured into water (60mL) and the suspension extracted with ethyl acetate (3x60mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated. The residue was purified by chromatography eluting with dichloromethane/ethyl acetate (3:1) to give the title compound as a yellow solid (0.116g, 27%).

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MH⁺ 395

NMR (CDCl₃) δ 8.32 (1H, dd, J=4 & 2Hz), 7.97 (2H, d, J=8Hz), 7.89 (1H, dd, J=9 & 2Hz), 7.54 (4H, m), 7.04 (1H, dd, J=9 & 4Hz), 6.88 (2H, d, J=9Hz), 1.43 (3H, t, J=7 Hz)

Ref: ¹ R. Miyaura et al J.Org.Chem.,1995,60,7508-7510.

Example 2.76-Difluoromethoxy-2-(3-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine5 (i) 1-(2,2-Dibromo-vinyl)-3-fluoro-benzene

To a stirred cooled (ice/salt, 0°) solution of carbon tetrabromide (48.82g) in anhydrous CH₂Cl₂ (200mL) was added portionwise over 3 minutes, triphenylphosphine (77.1g), maintaining the temperature below 10°. The resulting orange suspension was stirred at 0° for 1 hour before adding to it, 3-fluorobenzaldehyde (7.8mL). After the addition was complete, the suspension was stirred at 0° for 1 hour then quenched by the addition of water (75mL). The organic phase was separated and washed with brine (75mL), dried (Na₂SO₄) and evaporated to dryness. The residual gum was poured into cyclohexane (1L) and stirred for 30 minutes. The organic phase was decanted and the residue taken up into CH₂Cl₂ and poured into cyclohexane (1L). This procedure was repeated twice more and the combined organic phases concentrated to ~100mL and passed through silica gel. The filtrate was concentrated to give the title compound as a mobile yellow oil (24g, 100%).

MH⁺ 280, MH⁻ 279

NMR (CDCl₃) δ 7.05 (1H, tm, J= 9Hz) 7.3 (3H, m) 7.45 (1H, s)

20 (ii) (3-Fluoro-phenyl)-propynoic acid methyl ester

To a stirred solution of 1-(2,2-dibromo-vinyl)-3-fluoro-benzene (23.8g) in anhydrous THF (350mL) cooled to -78° was added dropwise over 30 minutes, n-butyllithium (2.2eq, 1.6M in hexanes). The mixture was stirred for a further 30 minutes at -78° before methyl chloroformate (11.6g, 9.5mL) was added and the resultant mixture allowed to warm to 0° for 1 hour before being diluted with 1:1 saturated aqueous sodium bicarbonate:ammonium chloride (100mL) and extracted into ether (2x 100mL). The combined organic extract was washed with brine (25mL), dried (Na₂SO₄) and evaporated to dryness to give the title compound as a brown oil (16.7g, 100%).

30 MH⁻ 173

NMR (CDCl₃) δ 7.4-7.1 (4H, m) 3.85 (3H, s, CO₂Me)

(iii) 2-(3-Fluoro-phenyl)-6-methoxy-pyrazolo[1,5-b]pyridazine-3-carboxylic acid methyl ester

35 1,8-Diazabicyclo[5.4.0]undec-7-ene (5mL) was added to a stirred, chilled, mixture of (3-fluoro-phenyl)-propynoic acid methyl ester (2.67g) and 1-amino-3-methoxy-pyridazin-1-ium mesitylene sulphonate (4.89g) in acetonitrile (80mL) and the mixture was stirred at 0° for 1 hour then at ambient temperature for 18 hours. The mixture was concentrated *in vacuo*, and partitioned between ethyl acetate (150mL) and water (150mL). The aqueous

phase was separated and further extracted with ethyl acetate (2x100mL). The combined organic extracts were washed with water (2 x 50mL), brine (25mL), dried (MgSO₄), filtered and evaporated *in vacuo* to give a solid which was triturated with anhydrous ether: petroleum ether (1:0.5) to give the title compound as a brown solid (2.4g, 53%).

5 MH⁺ 302

1H NMR (CDCl₃) δ 12.8 (1H, br s); 8.4 (1H, d, J 10Hz) 7.7-7.6 (2H, m) 7.42 (1H, q, J 8 Hz) 7.15 (1H, td, J 8 & 3Hz) 6.95 (1H, d, J 10Hz) 4.1 (3H, s) 3.88 (3H, s)

(iv) 2-(3-Fluoro-phenyl)-6-methoxy-pyrazolo[1,5-b]pyridazine-3-carboxylic acid

10 2N sodium hydroxide (50mL) was added to a solution of 2-(3-fluoro-phenyl)-6-methoxy-pyrazolo[1,5-b]pyridazine-3-carboxylic acid methyl ester (2.3g) in absolute ethanol (50mL) and the resulting mixture heated to reflux for three hours. The cooled reaction mixture was poured slowly into a stirred solution of 2N hydrochloric acid (300mL). The resulting suspension was stirred at ambient temperature for 1 hour then filtered and the filter cake
15 washed with water and dried *in vacuo* at 60° to give the title compound as an off-white solid (2.0g, 91%).

MH⁺ 288

1H NMR (DMSO) δ 8.45 (1H, d, J 10Hz); 7.67 (2H, m); 7.5 (1H, q, J 7Hz); 7.3 (1H, td, J 7 & 2Hz); 7.21 (1H, d, J 10Hz); 4.0 (3H, s)

20

(v) 3-Bromo-2-(3-fluoro-phenyl)-6-methoxy-pyrazolo[1,5-b]pyridazine

To a stirred solution of 2-(3-fluoro-phenyl)-6-methoxy-pyrazolo[1,5-b]pyridazine-3-carboxylic acid (2.0g) in anhydrous DMF (20mL) was added n-bromosuccinimide (1.78g) and the resulting solution stirred at ambient temperature for 3 hours. The reaction mixture
25 was diluted with ethyl acetate (800mL) and washed sequentially with water (10x100mL) and sat. brine (25mL), dried (Na₂SO₄), and concentrated to give the title compound as a buff solid (2.1g, 93%).

MH⁺ 323, MH⁻ 321

1H NMR (CDCl₃) 7.9 (2H, m) 7.8 (1H, d, J 10Hz); 7.45 (1H, m); 7.1 91H, td, J 8 & 2 Hz);
30 6.78 (1H, d, J 10Hz); 4.1 (3H, s)

(vi) 6-Difluoromethoxy-2-(3-fluoro-phenyl)-pyrazolo[1,5-b]pyridazine

Portions of 3-bromo-2-(3-fluoro-phenyl)-6-methoxy-pyrazolo[1,5-b]pyridazine (400mg, 2.1g total) were placed in individual Reactivials equipped with a magnetic stirrer bar.
35 Pyridine hydrochloride (10eq) was added to each vial, the vials sealed, and heated to 200° for 3 hours. The vials were allowed to cool to ~140° before opening and the contents poured into ice/water. The resulting mixture was extracted into ethyl acetate (3x100mL) and the combined organic extracts washed with water (7x75mL), dried (Na₂SO₄) and evaporated to give the des-bromo phenol as a brown solid (1.0g, MH⁺ 230).

This solid was dissolved in anhydrous DMF (10mL) and sodium hydride (60% dispersion in mineral oil, 200mg) added portionwise. After stirring for 20 minutes at ambient temperature the solution was transferred to a small cooled autoclave and bromodifluoromethane (5mL, xs, condensed at -30°) added. The autoclave was then sealed, allowed to warm to ambient temperature and stirred for 36 hours. The resulting solution was diluted with ethyl acetate (200mL), washed with water (10x20mL), dried (Na₂SO₄), concentrated and the residual gum purified by flash column chromatography with cyclohexane:ethyl acetate (4:1) as eluant. This gave the title compound as a solid (652mg, 60%).

5 MH⁺ 280 MH⁻ 278

NMR (DMSO) δ 8.42(1H, d, J= 10Hz) 7.85 (1H, d, J 8Hz) 7.78 (1H, t, J 70Hz) 7.55 (1H, q, J 8Hz) 7.38 (1H, s) 7.25 (1H, m) 7.17 (1H, d, J 10Hz)

(vii) 3-Bromo-6-difluoromethoxy-2-(3-fluoro-phenyl)-pyrazolo[1,5-b]pyridazine

15 N-bromo succinimide (195mg) was added to a solution of 6-difluoromethoxy-2-(3-fluoro-phenyl)-pyrazolo[1,5-b]pyridazine (251mg) and sodium bicarbonate (185mg) in anhydrous DMF (10mL) and stirred for 18h. The reaction mixture was diluted with ethyl acetate (300mL) and washed with water (10x20mL), brine (20mL), dried (Na₂SO₄) and concentrated to give the title compound as a solid (293mg, 91%).

20 MH⁺ 359, MH⁻ 356/357

NMR (DMSO) δ 8.36 (1H, d, J 10Hz) 7.88 (1H, d, J 8Hz) 7.78 (1H, t, J 70Hz, OCHF₂) 7.77 (1H, dm, J 10Hz) 7.62 (1H, dt, J 8 & 6Hz) 7.38 (1H, dt, J 9 & 2Hz) 7.3 (1H, d, J 10Hz)

(viii) 6-Difluoromethoxy-2-(3-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine

25 To a stirred solution of 3-bromo-6-difluoromethoxy-2-(3-fluoro-phenyl)-pyrazolo[1,5-b]pyridazine (286mg) in DMF(20mL) was added 2N aq sodium carbonate (10mL). To this mixture was added 4-methanesulfonyl-phenylboronic acid (180mg) and tetrakis triphenylphosphine palladium (0) (34mg). The resulting mixture was stirred and heated to reflux for 18 hours. The cooled reaction mixture was diluted with ethyl acetate (300mL) and the organic solution washed with water (10x30mL) and brine (30mL), dried (Na₂SO₄) and evaporated to give a gum which was purified by flash column chromatography with chloroform:ethyl acetate (50:1 to 5:1) as eluant. Combination of appropriate fractions and concentration gave the title compound as an off-white solid (132mg, 37%).

35 MH⁺ 434

¹H NMR(CDCl₃) δ 8.02 (1H, d, J 9Hz); 7.95 (2H, d, J 10Hz); 7.58 (1H, d, 9Hz); 7.52 (1H, t, J 70Hz); 7.32 (3H, m); 7.08 (1H, m); 6.9 (1H, d, J 9Hz); 3.15 (3H, s)

EXAMPLE 3

Preparation of Compounds of formula (III)

Compounds of formula (III) may be prepared by any method described in WO 2004/024691 and equivalent patent applications.

5

Example 3.1

N-cyclohexyl-4-(trifluoromethyl)-6-[4-(methylsulfonyl)phenyl]pyridine-2-amine

(i) 2-[4-(methylthio)phenyl]-4-(trifluoromethyl)-pyridine

10 To a mixture of 2-chloro-4-(trifluoromethyl)pyridine (19.9g, 0.11mol), 4-(methylthio)phenylboronic acid (21.9g, 0.13mol), 1M aqueous sodium carbonate (180mL) and 1,2-dimethoxyethane (270mL) under an atmosphere of nitrogen was added palladium *tetrakis*triphenylphosphine (3.78g, 3.3mmol) and the reaction heated at 100°C for 14 hours. After cooling and concentration *in vacuo*, the residue was partitioned between ethyl acetate (350mL) and water (400mL) and separated. The aqueous layer was further
15 extracted with ethyl acetate (2 x 150mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Filtration through a pad of silica gel (200g) eluting with a gradient of ethyl acetate in cyclohexane gave the title compound (29.4g) LC retention time 3.62mins, MS m/z 269 (MH⁺).

20 (ii) 2-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-pyridine

To a stirred suspension of intermediate (i) (29.4g, 0.11mol) in methanol (400mL) at 0°C was added portionwise a suspension of Oxone™ (134g) in water (200mL). The reaction was warmed to room temperature and stirred for 14 hours. The methanol was removed *in vacuo* and the residue diluted with saturated aqueous sodium bicarbonate (2L) and
25 extracted with ethyl acetate (3 x 1L). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give the title compound (32g, 0.106mol) LC retention time 2.90, MS m/z 302 (MH⁺)

(iii) 2-Chloro-4-(trifluoromethyl)-6-[4-(methylsulfonyl)phenyl] pyridine

30 To a solution of intermediate (ii) (32g, 0.106mol) in dichloromethane (400mL) at reflux was added 3-chloroperbenzoic acid (41.7g of 57 to 86% grade material) portionwise over 15 minutes. After stirring for 14 hours at reflux, the reaction was cooled, diluted with dichloromethane (2L) and washed sequentially with saturated aqueous sodium bicarbonate solution, saturated aqueous sodium sulfite solution containing tetra-n-butylammonium sulfate (4mL) and water, dried over sodium sulfate and concentrated *in vacuo* to give 2-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-pyridine-N-oxide (37.2g, containing traces of a tetra-n-butylammonium salt) LC retention time 2.34, MS m/z 318 (MH⁺). A mixture of this crude material and phosphorus oxychloride (110mL) was heated at 110°C for 4 hours. After cooling, the majority of the phosphorus oxychloride was
35

removed *in vacuo* and the residue neutralised with saturated aqueous sodium bicarbonate solution (300mL), with cooling. The mixture was extracted with chloroform and the combined organic extracts dried over sodium sulfate and concentrated *in vacuo*. The residue was recrystallised from 2-propanol to give the title compound (22.0g) LC retention time 3.23 min, MS m/z 336/338 (MH⁺).

(iv) N-cyclohexyl-4-(trifluoromethyl)-6-[4-(methylsulfonyl)phenyl]pyridine-2-amine

A stirred mixture of intermediate (iii) (6g, 17.8mmol) and cyclohexylamine (175mL) was heated at 110°C for 14 hours. After cooling, the reaction was diluted with water (1L), acidified with 2N HCl (750mL) and filtered to give the title compound (6.48g) LC retention time 3.81mins MS m/z 399 (MH⁺); ¹H-NMR (CDCl₃) δ 1.22-1.86 (8H, m), 2.60-2.16 (2H, m), 3.09 (3H, s), 3.67-3.78 (1H, m), 4.84 (1H, d, J = 7Hz), 6.57 (1H, s), 7.19 (1H, s), 8.03 (2H, d, J = 9Hz), 8.17 (2H, d, J = 9Hz).

Example 3.2

2-[4-(methylsulfonyl)phenyl]-6-[(2-pyridinylmethyl)oxy]-4-(trifluoromethyl)pyridine

(i) 4-(Trifluoromethyl)-6-[4-(methylthio)phenyl]-2-pyridone

To a stirred solution of diisopropylamine (11.5mL, 81.8mmol) in THF (75mL) at 0°C was added n-butyllithium (51.1mL of a 1.6M solution in hexanes, 81.8mmol). After stirring for 15 minutes, a solution of 4,4,4-trifluoro-3-methyl-2-butenic acid (6.0g, 38.9mmol) in THF (10mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 30 minutes before being cooled to 0°C and treated dropwise with a solution of 4-(methylthio)benzonitrile (2.91g, 19.5mmol) in THF (10mL). Upon complete addition, the reaction was heated at reflux for 14 hours. After cooling, water (200mL) was added and the mixture extracted with ethyl acetate (250mL). The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo* and the resulting residue purified by silica chromatography eluting with 1:1 ethyl acetate / cyclohexane to give the title product (2.43g) LC retention time 3.10mins MS m/z 286 (MH⁺).

(ii) 4-(Trifluoromethyl)-6-[4-(methylsulfonyl)phenyl]-2-pyridone

To a stirred mixture of intermediate (i) (2.43g, 8.52mmol) in methanol (100mL) at 0°C was added portionwise a suspension of Oxone™ (15.7g, 25.6mmol) in water (60mL). The reaction was warmed to room temperature and stirred for 14 hours. The methanol was removed *in vacuo* and the resulting residue partitioned between saturated aqueous sodium bicarbonate (500mL) and chloroform (200mL) and separated. The aqueous layer was further extracted with chloroform (3 x 100mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated to give the title compound (1.72g) LC retention time 2.57mins, MS m/z 318 (MH⁺).

(iii) 2-[4-(methylsulfonyl)phenyl]-6-[(2-pyridinylmethyl)oxy]-4-(trifluoromethyl)pyridine

Diisopropylazodicarboxylate (0.93mL, 4.7mmol) was added dropwise to a solution of intermediate (ii) (1g, 3.2mmol), 2-pyridinylmethanol (0.38mL, 3.9mmol) and triphenylphosphine (1.24g, 4.7mmol) in chloroform (80mL). After stirring for 14 hours, the reaction was concentrated and the residue diluted with methanol and loaded onto a methanol-conditioned 10g Varian bond-elut SCX-2 cartridge. The cartridge was washed with methanol (2 x 40mL) followed by a solution of 9:1 methanol/2N hydrochloric acid. The combined acidic fractions were concentrated and the residue triturated with methanol to give the title compound as its hydrochloride salt (348mg) LC retention time 3.35mins, MS m/z 409 (MH⁺); ¹H-NMR (d₆-DMSO) δ 3.28 (3H, s), 5.79 (2H, s), 7.47 (1H, s), 7.64 (1H, t, J = 6Hz), 7.85 (1H, d, J = 8Hz), 8.03 (2H, d, J = 9Hz), 8.11 (1H, s), 8.17 (1H, t, J = 8Hz), 8.38 (2H, d, J = 9Hz), 8.75 (1H, d, J = 6Hz)

Example 3.3

4-methyl-N-[(1-methyl-1H-pyrazol-4-yl)methyl]-6-[4-(methylsulfonyl)phenyl]-2-pyridinamine

(i) 4-Methyl-6-[4-(methylthio)phenyl]-2-pyridone

To a stirred solution of lithium diisopropylamide (50mL of a 2M solution in heptane/THF/ethyl benzene, 0.1mol) in THF (50mL) at -78°C and under an atmosphere of nitrogen was added dropwise a solution of 3-methyl-2-butenic acid (5g, 0.05mol) in THF (50mL). The reaction was warmed to 0°C for 30 minutes. After cooling to -78°C, a solution of 4-(methylthio)benzonitrile (7.45g, 0.05mol) in THF (50mL) was added dropwise. Upon complete addition, the reaction was warmed to room temperature and stirred for 3 hours. Water (150mL) and ethyl acetate (100mL) were added to the reaction mixture and the resulting precipitate filtered, washed with ethyl acetate and dried to give the title compound (4.96g, 43%) LC retention time 2.75mins, MS m/z 232 (MH⁺).

(ii) 4-Methyl-6-[4-(methylsulfonyl)phenyl]-2-pyridone

To a stirred mixture of intermediate (i) (3.7g, 16.0mmol) in methanol (150mL) at 0°C was added portionwise a suspension of Oxone™ (29.5g, 48.0mmol) in water (100mL). The reaction was warmed to room temperature and stirred for 14 hours. The methanol was removed *in vacuo* and the resulting residue partitioned between saturated aqueous sodium bicarbonate(1L) and chloroform (500mL) and separated. The aqueous layer was further extracted with chloroform (3 x 200mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated to give the title compound (3.20g, 76%) LC retention time 2.20mins, MS m/z 264 (MH⁺).

(iii) 4-Methyl-6-[4-(methylsulfonyl)phenyl]pyridine-2-trifluoromethanesulfonate

To a stirred solution of intermediate (ii) (3.20g, 12.2mmol) in pyridine (150mL) at 0°C and under an atmosphere of nitrogen was added dropwise trifluoromethanesulfonic anhydride (2.46mL, 14.6mmol). After stirring for 1hr at 0°C, the pyridine was removed *in vacuo* and the residue partitioned between water (200mL) and dichloromethane (200mL). The layers were separated and the aqueous phase further extracted with dichloromethane (3 x 100mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give the title compound (4.27g, 89%) LC retention time 3.48mins, MS m/z 396 (MH⁺).

10 (iv) N-[(1-methyl-1H-pyrazol-4-yl)methyl]-4-methyl-6-[4-(methylsulfonyl)phenyl]pyridine-2-amine

A stirred solution of intermediate (iii) (1.25g, 3.15mmol) and (1-methyl-1H-pyrazol-4-yl)methylamine (0.70g, 6.30mmol) in NMP (10mL) was heated at 180°C for 14 hours, cooled, and loaded evenly onto 5 methanol-conditioned 10g Varian bond-elut SCX-2 cartridge. The cartridges were washed with methanol (2 x 40mL each) followed by a solution of 9:1 methanol/concentrated ammonium hydroxide (2 x 40mL each). The ammoniacal fractions were concentrated and purified by silica chromatography eluting with a gradient of cyclohexane to ethyl acetate to give the title compound (780mg) LC retention time 2.32mins, MS m/z 357 (MH⁺); ¹H-NMR (CDCl₃) δ 2.23 (3H, s), 3.09 (3H, s), 3.88 (3H, s), 4.47 (2H, d, J = 6Hz), 4.68 (1H, br), 6.28 (1H, s), 6.99 (1H, s), 7.36 (1H, s), 7.50 (1H, s), 8.00 (2H, d, J = 9Hz), 8.19 (2H, d, J = 9Hz).

EXAMPLE 4
Biological Data

25 Inhibitory activity against human COX-1 and COX-2 was assessed in COS cells which had been stably transfected with cDNA for human COX-1 and human COX-2. 24 Hours prior to experiment, COS cells were transferred from the 175cm² flasks in which they were grown, onto 24-well cell culture plates using the following procedure. The incubation medium (Dulbecco's modified eagles medium (DMEM) supplemented with heat-inactivated foetal calf serum (10%v/v), penicillin (100 IU/ml), streptomycin (100µg/ml) and geneticin (600µg/ml)) was removed from a flask of confluent cells (1 flask at confluency contains approximately 1x10⁷ cells). 10ml of phosphate buffered saline (PBS) was added to the flask to wash the cells. Having discarded the PBS, cells were then rinsed in 10ml trypsin for 20 seconds, after which the trypsin was removed and the flask placed in an incubator (37°) for 1-2 minutes until cells became detached from the flask. The flask was then removed from the incubator and cells resuspended in 10ml of fresh incubation medium. The contents of the flask was transferred to a 250ml sterile container and the volume of incubation medium subsequently made up to 100ml. 1ml cell suspension was

pipetted into each well of 4x24-well cell culture plates. The plates were then placed in an incubator (37°C, 95% air/5% CO₂) overnight. If more than 1 flask of cells were required, the cells from the individual flasks were combined before being dispensed into the 24-well plates.

- 5 Following the overnight incubation, the incubation medium was completely removed from the 24-well cell culture plates and replaced with 250µl fresh DMEM (37°C). The test compounds were made up to 250x the required test concentration in DMSO and were added to the wells in a volume of 1µl. Plates were then mixed gently by swirling and then placed in an incubator for 1 hour (37°C, 95% air/5% CO₂).
- 10 Following the incubation period, 10µl of arachidonic acid (750µM) was added to each well to give a final arachidonic acid concentration of 30µM. Plates were then incubated for a further 15 minutes, after which the incubation medium was removed from each well of the plates and stored at -20°C, prior to determination of prostaglandin E₂ (PGE₂) levels using enzyme immunoassay. The inhibitory potency of the test compound was expressed as an IC₅₀
- 15 value, which is defined as the concentration of the compound required to inhibit the PGE₂ release from the cells by 50%. The selectivity ratio of inhibition of COX-1 versus COX-2 was calculated by comparing respective IC₅₀ values.

The following IC₅₀ values for inhibition of COX-2 and COX-1 were obtained for compounds of the invention:

20

Compound No.	COX-2: IC ₅₀ (nM)	COX-1: IC ₅₀ (nM)
1.1	<1	81,300
1.2	23	9,675
1.3	4	2,923
1.5	6	61,380
2.1(v)	35	>100,000
2.2(ii)	<10	3,880
2.3(ii)	3	>100,000
2.4(iii)	370	>100,000
2.5	21	>100,000
2.6(iv)	0.44	3828
2.7(viii)	16	>55,200

Example 5
Microsomal Assay

Inhibitory activity against microsomal h-COX2 was assessed against a microsomal preparation from baculovirus infected SF9 cells. An aliquot of microsomal preparation was thawed slowly on ice and a 1/40,000 dilution prepared from it into the assay buffer (sterile water, degassed with argon containing 100mM HEPES (pH 7.4), 10mM EDTA (pH7.4), 1mM phenol, 1mM reduced glutathione, 20mg/ml gelatin and 0.001mM Hematin). Once diluted the enzyme solution was then sonicated for 5 seconds (Branson sonicator, setting 4, 1cm tip) to ensure a homogeneous suspension. 155µl enzyme solution was then added to each well of a 96-well microtitre plate containing either 5µl test compound (40x required test concentration) or 5µl DMSO for controls. Plates were then mixed and incubated at room temperature for 1 hour. Following the incubation period, 40µl of 0.5µM arachidonic acid was added to each well to give a final concentration of 0.1µM. Plates were then mixed and incubated for exactly 10 minutes (room temperature) prior to addition of 25µl 1M HCl (hydrochloric acid) to each well to stop the reaction. 25µl of 1M NaOH (sodium hydroxide) was then added to each well to neutralise the solution prior to determination of PGE₂ levels by enzyme immunoassay (EIA).

The following IC₅₀ values for inhibition of COX-2 and COX-1 were obtained from the microsomal assay for compounds of the invention:

Example No.	COX-2: IC ₅₀ (nM)	COX-1: IC ₅₀ (nM)
1.6	<10	3,752
1.7	<10	79,889
1.8	<10	1,860
1.9	22	69,000
1.10	22	>30000

Examples 3.1, 3.2, 3.3 had IC₅₀ values for inhibition of COX-2 of 0.5µM or less and at least a 100-fold selectivity for COX-2 over COX-1, based on comparison of the respective IC₅₀ values.

EXAMPLE 6

Patient study

In the following, the invention will be discussed in more detail with reference to a patient study. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as

disclosed herein. The results of the patient study are graphically represented in the attached figures, which will be discussed in more detail in the following.

- 5 The study may be performed as a multicenter, double-blind, placebo controlled randomised, parallel group determination of efficacy of compound 1-3 in combination with risperidone vs risperidone with placebo.

- 10 The patients may receive 2-6 mg/day of risperidone (Risperdal (E)), and, depending on which group they belonged, a therapeutically effective amount 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine once daily or placebo over 12 weeks after a brief wash-out period of earlier antipsychotic medication.

During the wash-out period, a benzodiazepine preparation (mostly lorazepam) may be prescribed, if necessary. Patients with agitation, anxiety, or sleeping problems may be also medicated with lorazepam during the study.

- 15 Efficacy and tolerability of the compound 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine /risperidone vs placebo/risperidone will be assessed using the following endpoints – positive and negative syndrome scale (PANSS), Clinical Global Impression score (CGI), AIMS, Simpson and Angus, Barnes Akathisia, Calgary
20 Depression Scale and cognition endpoints.

The use of biperiden may be monitored as a possible indicator for side effects of the antipsychotic medication.

- 25 In order to exclude the chance that possible differences in the therapeutic effectiveness between the two groups might be due to non-compliance during the risperidone therapy or to differences in risperidone metabolism, the plasma levels of risperidone or 9-OH-risperidone may be monitored during the study.

- 30 The statistics may be performed according to the criterion of "last observation carried forward" (LOCF), i. e., the last PANSS scores of the patients who dropped out before the end of the study were carried forward to all subsequent observation days.

For the comparison of the main efficacy parameter, the mean change in the PANSS between the two treatment groups, t-tests for independent samples may be employed.

- 35 With reference to the underlying hypothesis of a better outcome of the compound 1-3 risperidone group, a significance of $p < 0.05$ may be calculated in the one-tailed t-test and used as the basis for the estimation of the sample size (statistical power) and for the comparison of the groups. For all other comparisons, two-tailed t-tests may be used.

The improved effectiveness of the combination therapy with 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine /risperidone in comparison to risperidone monotherapy may be clearly shown by the significantly lower PANSS global scores after the 2nd to 12 weeks of treatment.

5

Therefore, it could be excluded that the observed differences in the therapeutic effectiveness between the two groups may be due to incompatibility during the risperidone therapy or differences in risperidone metabolism.

10 The combination of 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine /risperidone and risperidone according to the present invention may show improved results compared to the monopreparation risperidone with regard to effectiveness in the treatment of schizophrenia.

15 The combination of COX-2 inhibitor as defined above and risperidone according to the present invention thus may show improved results compared to the monopreparation risperidone with regard to effectiveness in the treatment of schizophrenia.

20 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

25 It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein.

30 They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims: